

Socioeconomic Stress by
Dopamine Receptor 2 Gene Interactions in
the Development of Obesity

by

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Dissertation submitted in partial fulfillment of
the requirements for the degree of Doctor of Philosophy in the Department of
Psychology and Neuroscience in the Graduate School
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ABSTRACT

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Abstract

Background: Previous research suggests that early life socioeconomic stress and certain genetic polymorphisms may be partly associated with increased adiposity; however, research on both genetic and environmental predictors fail to account for the dramatic increase in obesity over that last several decades. Hypothesis: It was hypothesized that a GxE interaction between DRD2-related SNPs and parental education would predict trunk and total fat mass. This same interaction would also predict total calories from a 24-hour diet recall, which would mediate its effect on trunk and total fat mass. Sample: The current study analyzed genetic and psychosocial data from 697 participants collected for the Family Heart Study, an investigation examining the relationship between psychosocial behaviors and cardiovascular risk factors. Methods: Interactions were assessed between four single nucleotide polymorphisms (SNPs) in the D2 receptor and ANKK1 genes and tertiles of parental education predicting DXA-scan-measured trunk and total body fat mass. A measure of total calories, as assessed by a 24-hour diet recall, was tested as a mediator of this effect. Results: An interaction between mother's education and RS1116313 SNP predicted trunk fat ($F(4,191)=2.94$, $p=0.022$) and total body fat ($F(4, 191)=3.94$, $p=0.004$). The effects were driven by a reduction in trunk and total fat mass among C/C or T/T homozygotes with a high mother's education, which was not observed among C/T heterozygotes. Father's education was neither an interactive nor a main effect predictor in any models. Interactions predicting total calories were also non-significant, and no support for mediation was found. Post-hoc analyses revealed that leisure activity was also not a mediator. Alternatively, certain dietary components were predicted by the interactions between mother's education and RS1124492 and between mother's education and RS1800498. Conclusions: Trunk and

total body fat composition are predicted by an interaction between mother's education and the RS1116313 SNP. This effect does not appear to be mediated by total calories or leisure activity. Other SNPs associated with the D2 receptor gene interact with mother's education to predict dietary components.

Dedication

This dissertation is dedicated to my loving parents and sister who have supported me from the very beginning. I dedicate this document to my amazing partner Jacqueline Mahendra, who has helped me throughout the challenging parts and the very fun parts too. I dedicate this document also to my closest friends Gregory Jaboin, MBA, Carlos Mariscal, MA and Pedzisayi Makumbe, PhD, without whose help I could have never gotten this far.

Contents

Abstract.....	iv
List of Tables	x
List of Figures	xii
Acknowledgements	xiii
1. Introduction	1
1.1 Obesity Research.....	1
1.2 GxE Effects in Obesity Research.....	4
2. Early Life Socioeconomic Stress.....	7
2.1 Stress as an Environmental Determinant.....	7
2.1 Early Life Socioeconomic Stress	8
2.2 Childhood Conditions Predict Obesity in Adulthood	13
2.3 Limitations.....	16
3. Eating Behavior as a Mediator of Stress Effect	18
3.1 Animal Studies.....	22
3.2 Human Studies	24
4. Genetic Effects on Obesity	28
5. DRD2 as a Genetic Determinant of Obesity	31
5.2 DRD2 and Obesity Overview	35
5.3 DRD2 Associated with Behavioral Mediators of Obesity	37
5.4 Stress as Moderator of DRD2 Activity	39
6. GxE Interactions in Obesity	42
7. Dissertation Methodology	44
7.1 Study Design and Sample	45

7.2 Variables	45
7.2.1 Environmental Predictors	45
7.2.2 Genetic Predictors	46
7.2.3 Total Calories as Mediator	50
7.2.4 Obesity Outcome	50
7.2.5 Covariates	52
7.3 Procedure	53
7.3.1 Database Management	53
7.3.2 Description of Analysis.....	54
7.3.3 Covariate Analysis	56
7.3.4 Mediation Analysis	60
7.4 Statistical Analysis.....	62
7.4.1 Distribution of Variables	62
7.4.2 Significance Testing.....	65
8. Results.....	67
8.1 Descriptive Statistics	67
8.2 Multicollinearity	72
8.3 Interaction Effect Analyses.....	72
8.3.1 Mother's Education x Genotype Predicts Calorie Consumption	73
8.3.2 Mother's Education x Genotype Interaction Predicts Trunk Fat.....	75
8.3.3 Mother's Education x Genotype Predicts Total Fat.....	77
8.4 Mediation Analysis	79
8.5 Post-Hoc Analyses.....	80
8.5.1 Predicting Leisure Activity For the RS116313 Genotype.....	80
8.5.2 Predicting Dietary Components For All Genotypes	81

8.5.4 SNP Proxy Search For RS1116313 SNP	85
9.1 RS1116313 by Mother's Education Interaction Predicts Trunk/Total Fat	87
9.2 24-Hour Diet Recall Does Not Mediate Effects on Body Fat.....	90
9.3 DRD2 and Metabolism	92
9.4 RS1800497 and RS1124492 by Mother's Education Interactions Predict Dietary Components	94
9.5 Main Effect of Mother's Education on Body Fat.....	96
9.4 Limitations.....	98
9.5 Future Directions	101
9.6 Conclusions	103
10. References.....	104
11. Biography	129

List of Tables

Table 1: Selected Human Studies on the Effect of Various Types of Chronic Early Life Stress on Obesity	10
Table 2: Selection of Animal and Human Studies on the Mediating Factors Implicated in the Effect of Stress on Obesity	18
Table 3: Selection of Animal and Human Studies on the Role of DRD2 in Obesity	31
Table 4: List of DRD2 Tagging SNPs, Distribution Statistics, and SNPs Captured	48
Table 5: Results of Exploratory Factor Analysis	58
Table 6: Factor Loading of SES Stress and Other Stress Predictors on a Single Factor.....	59
Table 7: Parental Education Tertiles	66
Table 8: Descriptive Statistics	67
Table 9: Missing Genotype Data	68
Table 10: Hardy-Weinberg Equilibrium Chi-Sq Tests Stratified By Race.....	69
Table 11: Missing Data By Variable.....	70
Table 12: Model of Covariates Predicting Log of 24-Hour Total Calorie Intake	71
Table 13: Model of Covariates Predicting Trunk Fat	71
Table 14: Model of Covariates Predicting Total Body Fat.....	71
Table 15: Mother's Education by Genotype Interactions Fail to Predict Total Calorie Consumption	73
Table 16: Correlations Between Trunk Fat, Total Fat and Total Calories, Dietary Components.....	74
Table 17: Transformed and Non-transformed Total Calorie Variable Fails to Predict Body Fat.....	75
Table 18: Mother's Education by Genotype Interactions Predict Trunk Fat	75
Table 19: Mother's Education by Genotype Interactions Predict Total Body Fat	77
Table 20: Interaction Between Mother's Education and RS1116313 Fails to Predict Leisure Physical Activity.....	81

Table 21: Mother's Education By RS1800497 Interaction Predicts Percent of Calories from Dietary Fat.....	81
Table 22: Mother's Education by RS1800497 Predicts Percent of Calories from Protein..	82
Table 23: Mother's Education by RS1124492 Interaction Predicts Percent of Calories from Dietary Fat.....	84
Table 24: SNPs in High Linkage Disequilibrium with RS1116313.....	85

List of Figures

Figure 1: Mediational Model - Gene x Environment Interaction Predicting Obesity, Mediated by Eating Behavior	44
Figure 2: Scree Plot of Eigenvalues.....	57
Figure 3: Mediational Model	61
Figure 4: Histogram of '24-Hour Total Calories' Variable with Normal (Red) and Log-Normal (Green) Distribution Lines	62
Figure 5: Histogram of Log-Transformation of '24-Hour Total Calories' Variable with Normal (Red) and Log-Normal (Green) Distribution Lines.....	63
Figure 6: Mother's Education by RS1116313 Interaction Predicts Trunk Fat	76
Figure 7: Mother's Education by RS1116313 Genotype Interaction Predicts Total Fat.....	78
Figure 8: Mother's Education by RS1800497 Interaction Predicts Percent of Calories from Dietary Fat.....	82
Figure 9: Mother's Education by RS1800497 Interaction Predicts Percent of Calories from Protein.....	83
Figure 10: Mother's Education by RS1124492 Interaction Predicts Calories from Dietary Fat	84

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1. Introduction

1.1 Obesity Research

Once thought to be a problem affecting only high-income regions, obesity has become an epidemic in all parts of the United States, with large disparities among socioeconomic groups. In the US, 66% of adults meet criteria for overweight (BMI ≥ 25) or obesity (BMI ≥ 30 ; Agurs-Collins & Bouchard, 2008). Individual health risks linked to this disease include hypertension, type 2 diabetes, coronary heart disease, stroke, cancers (e.g., endometrial, breast, colon) and death. As one can imagine, the economic cost to our society is immense (Just & Payne, 2009).

Given the physical and economic costs of obesity, it is incumbent upon us to understand its determinants, both as a means of preventing future cases and also appropriately treating the overwhelming number of cases already present. In terms of etiology, obesity like cardiovascular disease and diabetes is considered a complex disorder that may have a number of intricate and interacting causes. Given decades of research, it appears that excess weight is unlikely to be the result of purely genetic or purely environmental causes (Permutt, Wasson, & Cox, 2005); it must be due at least in part to an interaction of multiple heritable and experiential factors (Hetherington & Cecil, 2010).

Genetic predispositions, for example, do not seem to account for the tripling in the prevalence of obesity in the last decade (Tamashiro, Terrillion, Hyun, Koenig, & Moran, 2009) nor can they account for the widely divergent body weights of genetically

similar ethnic groups who consume different diets (Wing, et al., 2001). Some researchers have suggested that assortative mating (e.g., over time those with similar body types may be more likely to mate) may explain some of the variance, but its effect is undoubtedly very complex and multifaceted (McAllister, et al., 2009). Moreover, increased assortative mating might only heighten an existing GxE effect if the particular genotype in question were thereby increasing in the population.

Likewise, environmental factors cannot alone account for interindividual differences in weight gain - for example, body weight gain in the Vermont overfeeding study varied among subjects and was below the expected weight gain based on an identical quantity of surplus calories ingested (Bouchard, 2008). Some researchers suggest that certain viruses or gut microflora may account for some of this variance, but this research is still in its infancy (Fernandez-Real, et al., 2006; McAllister, et al., 2009). Moreover, its ultimate effects may still be a function of gene x environment interactions that make some individuals more susceptible to obesity given both their specific genotype and also the type of diet eaten.

Ultimately, outcomes are most likely the result of a number of genetic, epigenetic, environmental, and behavioral factors (Agurs-Collins & Bouchard, 2008; Butte, 2009). Instead of arising from one common interacting pathway, obesity probably arises from a number of environmental exposure / genetic predisposition combinations. Therefore, GxE combinations are probably much more common sources of obesity than monogenetic causes, which in even large genome-wide association studies seeking SNPs linked to BMI, are unable to explain more than a very small proportion (<2%) of BMI variability (Swinburn, et al., 2011).

One putative reason for the recent dramatic increase in obesity cases may be that the interaction of two known risk factors may lead to an even greater risk than either of the individual gene or environmental exposures alone. This may be particularly true if either the genetic or environmental effect were suddenly affecting a greater percentage of the population.

For example, there is evidence that low socioeconomic status (SES) is consistently affecting greater numbers of people in the US (Norton & Ariely, 2011). If it was shown that a socioeconomic stress by genetic interaction predicted obesity, the increase in solely socioeconomic stress might contribute to a large increase in population obesity even if the main effects of socioeconomic status or genetic vulnerability alone were both non-significant. The complex interactions involved in GxE interactions will be discussed in more detail later in this document.

This proposal aims to provide the rationale for exploring a gene x environment interaction predicting obesity, a major health epidemic facing the developed and developing world. This document will first begin by reviewing socioeconomic stress as a prominent environmental factor in obesity. Next, physiological mediators of socioeconomic stress effects will be reviewed. Then, a brief review of the genetics of obesity will quickly move to a discussion of candidate genes within the neurotransmitter systems of interest. Next, a model will be proposed to explain how one might investigate the contribution of one particular gene x environment interaction to the development of obesity. Finally, the results and conclusions of one such investigation will be presented.

Currently limited within the obesity literature, research in GxE interactions may help to explain the mixed results present in both the extant environmental and genetic

literature on obesity. As demonstrated in the prior decades of research, methodological approaches for seeking main effects underlying weight gain and obesity have been largely futile. Regardless of whether one particular GxE interaction alone explains the increase in US obesity, this study hopes to provide a clearer picture of the various and complex origins of excess body weight. Only by incorporating measures of both environmental stressors as well as genetic predispositions to energy intake will future research ever hope to uncover the complex interactions that likely underlie the development of obesity.

1.2 GxE Effects in Obesity Research

Life stress appears to be a promising environmental variable in GxE obesity research for a number of reasons. As described in detail below, stress appears to be linked to obesity as an endpoint, but also activates behavioral and biological changes associated with the development of obesity. A more general measure of life stress such as SES may be particularly useful since these data are included in many large datasets and represent a reasonably objective index of lifetime stress, as elaborated below. In addition, other ways in which stress appears to moderate certain genetic effects in obesity will be discussed.

Later this document will show that, even in well-designed prospective studies, stress seems to predict the development of obesity somewhat inconsistently, with mixed evidence for Blacks and men in particular. Although this may seem to indicate that stress is not an overall predictor of obesity, mixed results would be expected if a GxE interaction were taking place. For example, if particular genetic factors moderate the

association between stress and obesity, then only when individuals are sensitive to stress exposure would they engage in behaviors or experience biological changes associated with the development of obesity. If stress were associated with obesity in only some cases, one might also expect stress to be associated with increased eating behavior in only some cases. Indeed, stress is also associated with decreased eating behavior in some cases and no change in others (Dallman, 2010).

Thus for some individuals, stress appears to predict obesity, as well as activating behavioral and biological changes associated with the development of obesity. Likewise, certain monoaminergic neurotransmitters have been associated with obesity, but also in regulating the energy intake behavior associated with developing obesity. Among the possible genes that might interact with the effect of stress, monoaminergic (e.g., serotonergic, dopaminergic) genes may provide ideal candidates for studying gene x environment interactions in obesity.

If indeed a GxE interaction were taking place, one might expect to find mixed results within monoaminergic genetic obesity research if a particularly relevant environmental exposure were taken into account within the analyses. For example, if a particular 'plasticity' gene (Belsky, et al., 2009) required a certain environment exposure to express different physical phenotypes (e.g., increasing adiposity), then as with research on the effect of stress on obesity, one might expect to observe mixed evidence supporting a link between a particular gene and obesity among studies taking stress exposure into account. Thus, the dopamine receptor 2 (DRD2) gene, that is found to have mixed associations with obesity and eating behavior, will be proposed as possible candidate for future study.

Favoring a conceptual model developed by Dallman and colleagues (2010) throughout years of scholarship, this proposal will postulate that stress, interacting with genetic predispositions, stimulates biological processes, which increase the motivation for eating and eventually lead to the development of obesity (Kyrou & Tsigos, 2009)

2. Early Life Socioeconomic Stress

2.1 Stress as an Environmental Determinant

In its most simplified explanation, obesity results from a long-term imbalance between energy intake and expenditure. When the former exceeds the latter, biological processes favor adipogenesis and expanded lipid storage (Agurs-Collins & Bouchard, 2008). Certain environmental factors preferentially favor increased energy consumption and decreased expenditure. Among such environmental factors, background stress in the form of low SES may be particularly instrumental for a subset of the population in increasing fat accumulation over time.

This section will first review the mixed evidence that SES stress is associated with obesity. Then, it will be demonstrated that, by ignoring genetic predispositions to eating behavior, research on the effect of socioeconomic stress on obesity may have been missing a critical piece. This omission may also explain the pattern of mixed results within the literature.

Stress, defined as a state of threatened homeostasis, mobilizes a complex and coordinated physiological and behavioral response that seeks to restore homeostasis to the organism. Stress can have an acute or a chronic effect; research suggests that chronic stressors may have a particularly profound and long-term effect on health (Evans & Kim, 2007; Kopp, Skrabski, Szekely, Stauder, & Williams, 2007). Some have suggested that the biological accumulation of visceral fat and visceral obesity may also be partially influenced by stress (Dallman, et al., 2004).

The impact of stress depends on a number of temporal and intensity-related factors. A greater lifetime exposure to stress may be associated with a greater effect on homeostatic processes (Geronimus, Hicken, Keene, & Bound, 2006). Moreover, different types or period-lengths of stress may have differing effects on these same homeostatic processes. Some research suggests that early life chronic stressors may have greater effects than other later chronic stressors (Singer & Ryff, 1999). One major type of stress investigated within the stress-obesity literature is SES-related stress.

2.1 Early Life Socioeconomic Stress

The American Psychological Association defines SES as a “combination of education, income, and occupation;” and it is often used to differentiate between individuals based on “social standing or class of an individual or group” (American Psychological Association, 2011, p. 1). Disadvantaged SES, for example, may result from a low education or a low parental education, a low income, or a low childhood household income.

Although not an acute stressor such as violence or a challenging mental task, SES is conceptualized by many as a more general lifetime stressor that affects individuals in a variety of ways. Moreover, low SES seems to predispose individuals to psychological and physical health risks that themselves may be associated with increased life stress. For example, low SES is related to low mastery and low sense of control (Lachman & Weaver, 1998), qualities that can predispose one to poor coping skills and future life stress. Low SES has also been shown to predict slower cardiovascular recovery (Steptoe, et al., 2002), greater diastolic blood pressure, and heart rate reactivity (E. Chen, Langer,

Raphaelson, & Matthews, 2004; Treiber, Harshfield, Davis, Kapuku, & Moore, 1999) to a mental stress task, indices which themselves are predictors of poor and potentially costly future health outcomes. These 'weathering' processes have been shown to prematurely age individuals from low SES backgrounds (Geronimus, 2000). Low SES has also been linked to greater circulating stress hormones and poor health behaviors in Blacks, Whites, older and younger individuals (Cohen, Doyle, & Baum, 2006).

Childhood SES may be particularly important since it appears to have effects that persist into adulthood. For example, low childhood SES is associated with increased mortality in adulthood independent of adult SES, suggesting the enduring impact of childhood adversity on adult health (Lynch, Kaplan, & Salonen, 1997). Finally, an additive effect of a gene and childhood SES has already been demonstrated to predict cardiovascular reactivity to mental stress (Williams, et al., 2008), suggesting that childhood SES may be a useful variable in GxE studies.

Early life stressors may be instrumental in a physiological cascade that some researchers suggest may culminate in adiposity. It is hypothesized that the interactive effect of genes and environmental exposure occur through epigenetic effects. In animal models, these epigenetic effects are known to occur primarily in early life stages (Curley, Jensen, Mashoodh, & Champagne, 2011). This early life period is also important in the later development of adiposity and metabolism in animals (Grove, Grayson, Glavas, Xiao, & Smith, 2005).

Since low childhood SES in humans co-occurs with a large variety of stressors such as a worse diet and nutrition, material hardships, psychosocial conditions of acute and chronic stress, overburdened or disrupted social supports, and toxic environmental

exposures, it is thought to be a proxy for many stressful life conditions (Geronimus, 2000). It is also thought to have a prolonged or greatly delayed effect upon the physical and/or emotional development of the individual (Singer & Ryff, 1999). Therefore, an early life stressor may be a particularly useful indicator of environmental exposure in GxE research.

As shown in **Table 1**, the literature supporting a link between SES-related stress and obesity is mixed. However as described earlier, mixed findings would be expected if a GxE interaction were present since the environmental factor would not be expected to predict obesity alone.

Table 1: Selected Human Studies on the Effect of Various Types of Chronic Early Life Stress on Obesity

Authors	Sample Size	Predictor Variables	Outcome Variables	Findings
<i>REVIEWS</i>				
(Sobal & Stunkard, 1989)	Review of 144 international published studies on SES and obesity	SES (most frequently income or education)	Obesity (BMI, body fat, skinfold thickness; dichotomous & continuous)	In industrialized nations, low SES led to greater obesity risk among women. Inconsistent among men, children. Direct relationship between SES and obesity among men, women, children in developing countries.
(Wang & Beydoun, 2007)	Meta-analysis of more than 80 publications published between 1990 and 2006.	Low-SES (low education)	Obesity (BMI)	Minorities and low SES are disproportionately affected with obesity in systematic review and meta-analysis of studies between 1990 and 2006 (p. 22). Annual increases per year range from 0.3 to 0.9 percentage points, although more complex patterns emerge when race taken into account. (Ex. high SES Black women exhibit more obesity than low SES Black women.)
(Senese,	Forty-eight	Childhood	Obesity (BMI)	Review reports inverse

Almeida, Fath, Smith, & Loucks, 2009)	publications based on 30 studies.	SES (parental education in all but 4 studies)	measured directly or self-reported)	associations found between childhood SES and adulthood obesity in 70% (14 of 20) of studies in females and 27% (4 of 15) in males.
(Gonzalez, Nazmi, & Victora, 2009)	Thirteen relevant articles were located (five cross-sectional and eight cohort)	Family socioeconomic status when the individual was five years or older.	Obesity (waist and hip circum., and/or WHR in adulthood)	Association between childhood poverty and abdominal obesity in review consistent in women, mixed in men.
(Tamayo, Christian, & Rathmann, 2010)	Thirteen studies met the meta-analysis inclusion criteria. Comprising 70,420 participants.	Low-SES (primarily parental occupation, then parental education, family income in 4 studies)	Obesity (BMI)	Review supported association between family income and father's occupation and overweight and obesity in women only. Parental education not linked to future obesity risk. Parental education had no direct or a small effect on obesity in six studies.
STUDIES				
(Flegal, Harlan, & Landis, 1988)	6,849 three successive cross-sectional national female samples	SES (Own education and household income)	Obesity (BMI and skinfold thickness)	In US sample of black and white women, both education and income negatively associated with BMI and skinfold thickness over 20y. Education stronger long-term predictor whereas income worse predictor over time.
(Sarlio-Lahteenkorva & Lahelma, 1999)	Finish Twin Cohort of over 6,000	Economic disadvantage (unemployment and low income)	Obesity (BMI)	Study reveals inverse association between economic advantage and obesity only among women. Direct association among some thin men.
(Molarius, et al., 2000)	Random prospective samples over 10y, 42000+ m/w (35-64y) (1979-1989) and 35000+ in final survey (1989-1996).	Education	Obesity (BMI)	Lower education associated with higher BMI in half of the male and all of the female populations, however, the male pattern came to resemble female pattern.
(Wardle, Waller, & Jarvis, 2002)	15,061 men and women	Years of education and economic	Obesity (BMI)	Obesity risk greater among men and women with fewer years of education and poorer

		conditions (i.e., gov't benefits, rent/own housing)		economic circumstances and among women of lower occupational status.
(Delva, O'Malley, & Johnston, 2006)	National sample of 62,156 eighth, 64,899 10th graders and 35,107 12th graders	SES (Based on both parents' education)	Obesity (BMI)	Prevalence of overweight and unhealthy behaviors greater among youth from racial/ethnic minority backgrounds, lower socioeconomic status, and in higher grades.
(Inagami, Cohen, Finch, & Asch, 2006).	2620 adults from 65 neighborhoods in Los Angeles County between 2000 and 2002.	Neighborhood disadvantage (based on % living below the poverty line, % of households headed by a female, male unemployment rate, and % of families receiving public assistance)	Obesity (BMI)	Individuals have higher BMI if they live in disadvantaged areas. Association partially explained by low proximity of grocery stores.
(Grafova, Freedman, Kumar, & Rogowski, 2008)	Nationally represent., longitudinal sample of 15,221 indiv. ≥ 55y	Neighborhood advantage (based on scales reflecting economic environment, the built environment, and the social environment.)	Obesity (BMI)	After controlling for individual- and family-level confounders, living in high SES neighborhood associated with a lower obesity for older men and women.
(Thornton, Bentley, & Kavanaugh, 2010)	2547 adults from 49 small-areas in Melbourne, Australia	Individual SES (education, occupation and income) and area SES (proportion of low-income households in each district)	Amount of fast food purchased for consumption at home	Results for area-level disadvantage were marginally non-significant after adjustment for individual-level characteristics, although increased fast food purchasing independently associated with lower education, being blue-collar employee and decreased household income.

Given decades of research into the contribution of SES on body shape and weight, several reviews and meta-analyses exist within the literature. An older review of international studies found that among Western countries, low SES was associated with greater obesity among women with less consistent patterns in men (Sobal & Stunkard, 1989). Since this review, many others below have corroborated the finding that particularly childhood SES is an important determinant of obesity. Although, as one review and meta-regression analysis of studies between 1990 and 2006 explains, even if a somewhat consistent overall pattern emerges in the literature that those with low SES and minorities are disproportionately affected with obesity, more complex patterns emerge when individual racial/ geographic groups are observed as described below (Wang & Beydoun, 2007).

2.2 Childhood Conditions Predict Obesity in Adulthood

Another important finding in this latter study that is echoed in others is the importance of childhood conditions in predicting obesity in adulthood. Wang and Beydoun (2007) report that about one third of obese preschool children and about one half of obese school-age children become obese adults. Moreover, the authors assert that “childhood and adolescence are key times for persons to form lifelong eating and physical activity habits” and therefore can set the stage for future lifetime body weight (Wang & Beydoun, 2007, p. 24). This review suggests that early life SES factors such as parental education might be a particularly meaningful for predicting future obesity. A series of other reviews and meta-analyses echo these general assertions, reporting that

low SES is often associated with obesity in later life (Gonzalez, et al., 2009; Senese, et al., 2009; Tamayo, et al., 2010).

Interestingly, in general these reviews tend to recall the earlier review that associations between childhood SES and obesity are found in both genders, but are stronger overall in women. For example, one study states that researchers found an inverse association between childhood SES and adulthood obesity in 70% (i.e., 14 of 20) of studies in females and 27% (i.e., 4 of 15) in males (Senese, et al., 2009). Another recent review found the association between SES and specifically abdominal obesity was also stronger in women (Gonzalez, et al., 2009).

Additional studies, some of which use large samples and prospective designs, come to similar conclusions. An earlier US longitudinal study of almost seven thousand female participants found that education was a strong predictor of obesity measured as BMI and skinfold thickness (Flegal, et al., 1988). A number of large national samples from Sweden, Finland, and England found a similar linear trend for SES predicting obesity in primarily or exclusively women, suggesting this pattern is not an exclusively US phenomenon (Kuskowska-Wolk & R., 1993; Martikainen & Marmot, 1999; Rissanen, M., Knekt, Reunanen, & A., 1991). Another study replicated these findings in older men and women, finding that economic advantage was protective against obesity (Grafova, et al., 2008).

It is important to note some mixed findings in the literature as well. As opposed to meta-analyses or reviews, some of the large epidemiological studies may be better equipped to conduct a fine-grained analysis of trends. For example, although an effect of SES on obesity was observed in one study, its effect was diminished by 20% when health

behaviors were controlled (Martikainen & Marmot, 1999). This suggests that perhaps the SES effect on obesity is partially explained by unhealthy behaviors.

As mentioned above, many studies found an effect either primarily or exclusively in women (Gonzalez, et al., 2009; Sarlio-Lahteenkorva & Lahelma, 1999; Senese, et al., 2009), whereas others found the effect irrespective of gender (Grafova, et al., 2008; Wang & Beydoun, 2007; Wardle, et al., 2002). It is notable that most of the articles suggesting an effect of gender are reviews, meta-analyses, or studies before 2000. It is suggested in some research projects that these conflicting gender findings may be the result of cohort effects. For example, one study comparing older survey data to more recent collections found that male obesity patterns are beginning to resemble female obesity patterns (Molarius, et al., 2000). If the pattern of male obesity is only recently beginning to resemble the pattern of women, as one paper intimates, then reviews compiling studies over a large period of time would not necessarily be able to observe this more recent change in prevalence.

One large US review found an overall effect of low SES on obesity but noted that in Black women, high SES was associated with greater obesity (Wang & Beydoun, 2007). This suggests that population trends may not accurately reflect patterns in all minority or demographic groups. For example, one study found that trends in obesity vary considerably by gender, racial/ethnic group, and age (Delva, et al., 2006).

In summary, it appears that many studies support a relationship between SES and obesity, but the direction and strength of the association does not necessarily hold for all racial, gender, age, or cohort subgroups. The relationship depends on a number of individual and neighborhood level characteristics. In all of the studies reviewed, SES has

been measured as current household income, occupation, and education as well as childhood household income, parental occupation, and parental education with similar outcomes with the exception of one review that reported that parental education was not a strong predictor of obesity in six studies (Tamayo, et al., 2010).

2.3 Limitations

Among developed countries including the US, there appears to be an inverse association between SES and obesity measured as BMI and skin thickness (McLaren, 2007). Interestingly enough, a positive relationship is observed in developing countries, suggesting that some other unmeasured environmental or biological variable may be influencing this association. Moreover, this review demonstrates that the inverse relationship between SES and obesity appears to be stronger among women in several studies and a few reviews, although one paper suggests that this relationship may strengthening among men.

It is important to note that none of the studies reviewed here take into account latent biological or genetic predispositions to pleasurable eating. Given the research suggesting the importance of variability in one's predisposition to stressful eating behavior, accounting for this variable is necessary. As presented in the next section, some research shows that stress is only associated with increased eating among a subset of individuals – about 40% of the population increases eating behavior, about 40% decreases eating behavior and about 20% does not change eating behavior according to Dallman (2010). Given that biological variables were not considered in these studies;

therefore, one would expect the type of mixed results observed in this literature. The importance of genetic moderators will be discussed later in this document.

3. Eating Behavior as a Mediator of Stress Effect

The previous section reviewed mixed research on the role of stress in the accumulation of excess weight. Some research suggests that the effect of stress on obesity is mediated through increased eating behavior, particularly of energy-dense ‘comfort foods.’ Among other researchers, Dallman and colleagues have led the exploration in this area in both human and murine studies as shown in **Table 2**.

Table 2: Selection of Animal and Human Studies on the Mediating Factors Implicated in the Effect of Stress on Obesity

Authors	Sample Size	Predictor Variables	Outcome Variables	Findings
<i>ANIMAL STUDIES</i>				
(Pecoraro, Reyes, Gomez, Bhargava, & Dallman, 2004)	Male Sprague-Dawley rats	Access to energy-dense lard and sucrose (comfort food) chow or chow alone. Restrained half of the rats in each group for 5 d (3 h/d).	Food intake. HPA axis response.	Stressed rats given a choice of lard, sucrose, or chow increased intake of both sucrose and lard compared to intake of chow. HPA response to restraint reduced in the stressed-comfort-food group.
(Petro, et al., 2004)	Male C57BL/6J mice	High fat, low fat, high-fat-restricted diet (i.e., mice fed equal calories of low fat diet with food high in fat)	Body fat, body weight	Mice on a calorie-restricted but proportionally high-fat diet developed high body fat and overall obesity within 3 weeks compared to those in low-fat diet.

(la Fleur, Houshyar, Roy, & Dallman, 2005)	Male Sprague Dawley rats	Compared 7-d feeding of lard chow (choice) or 50% lard-chow mixture (no-choice) and to chow only. All rats exposed to 30 min restraint on day 7.	Food intake, HPA axis response.	Stressed rats with choice composed diets with 50 – 60% total calories from lard. Choice of energy-dense calories strongly damps HPA response to stress. Without choice, energy-dense diet ineffective.
(Teegarden & Bale, 2008)	Male corticotropin-releasing factor receptor-2 deficient (stress-sensitive) mice & controls.	Mice were stressed and placed into groups given free or restricted access to high fat, high protein, high carb food	Food intake, HPA axis response.	Overall mice increased the percent of calories obtained from a high fat diet, as well as their overall caloric intake during stress. Reduced weight gain and caloric efficiency in stress-sensitive mice during stress and unrestricted food access. With restricted high fat access, stress increased (binge-like) fat consumption.
(Foster, et al., 2009)	Male Sprague-Dawley rats	Prior access to chow-only, sucrose / chow, lard / chow, or, sucrose / lard / chow diets	Central corticotropin-releasing factor (CRF) expression in rats measured 15 and 240 min after restraint.	Fat deposits increased by prior access to palatable food. Decrease in HPA activation following palatable food consumption. Neuroendocrine and autonomic outflows decreased by palatable calorie increase.

HUMAN STUDIES				
(Oliver, Wardle, & Gibson, 2000).	68 healthy men and women	Stressed and non-stressed groups given ad libitum meal with sweet, salty, or bland high- and low-fat foods.	Food intake	Stressed emotional eaters ate more sweet high-fat foods and a more energy-dense meal than unstressed and nonemotional eaters
(Wardle, Steptoe, Oliver, & Lipsey, 2000)	Ninety staff members (58 women and 32 men) of department store	Work stress (indexed by hour worked in past week over the past 7 days.	Food intake	High-workload periods associated with higher energy and saturated fat and sugar intake. There was a significant moderating effect of restrained eating which led to greater intake.
(Epel, Lapidus, McEwen, & Brownell, 2001)	59 healthy pre-menopausal women	Counter-balanced stress and control days	Food intake, types of food consumed	Greater negative mood associated with greater consumption.
(Macht, Roth, & Ellgring, 2002)	24 Male subjects	Film clips designed to induce anger, fear, sadness and joy	Chocolate intake	Joy increased and sadness decreased appetite for chocolate.
(Epel, et al., 2004)	131 medical students	Self-reported type of eater (stress eater vs. faster) and control vs. stressful exam days	Weight, self-reported food intake	36% were self-described stress-eaters. They tended to gain more weight during exam periods. 34% were stress-fasters.
(Gluck, Geliebter,	22 obese	Cold	Cortisol	Higher morning basal

Hung, & Yahav, 2004)	females (11 w/binge eating disorder, 11 w/o)	pressor stress task	levels	cortisol levels, greater cortisol increases, greater stress-related hunger and desire-to-binge ratings in obese women with BED.
(Raynor, Jeffery, Phelan, Hill, & Wing, 2005)	2237 weight-loss maintainers at a clinic	Variety of food consumed	Weight lost, energy intake	Decreases in variety of high-fat foods and increases in variety of healthy foods associated with lower intake and greater weight loss.
(Zellner, et al., 2006)	2 Studies (1. 34 female undergrads , 2. 169 m/f undergrads)	1. Healthy / unhealthy food choices following stressor. 2. Survey on eating	1. & 2. Food intake	Stress causes preference for less healthy, high fat foods (M&Ms) and reduces preference for healthy low fat foods (grapes). More females than males increase food consumption when stressed. More restrained eaters (i.e., dieters; 71%) increase eating when stressed than people who undereat or who do not change eating when stressed (35%).
(George, Khan, Briggs, & Abelson, 2010)	Fourteen subjects (8 females, 6 males) aged 18—42	Injections of placebo and corticotropin-releasing hormone	Food intake, HPA axis response	Subjects ate more following CRH than placebo and peak cortisol response to CRH was strongly related to both caloric intake and total consumption.

In her review, Dallman (2010) reports that among the 40% that increase feeding behavior in times of stress, both humans and animals shift toward choosing more pleasurable and/or palatable calories. These ‘comfort foods’ tend to include large amounts of fat and sugar, amounting to energy-dense food consumption even when individuals have no caloric needs or hunger to speak of. Even in highly controlled lab

environments, acute physical or emotional distress induces intake of 'comfort' foods that are pleasurable to consume in humans and animals.

3.1 Animal Studies

A number of animal studies have explored the process by which stress effects are mediated by changes in eating behavior. A common pattern of findings suggests that stressed rodents may alleviate hypothalamic-pituitary-adrenal (HPA) activation and stress responses by increasing consumption of fatty and sugary 'comfort' foods. For example, one study found that stressed rats given a choice of lard, sucrose, or chow increased intake of both sucrose and lard compared to intake of chow (Pecoraro, et al., 2004). In turn, HPA response to the stressor was reduced in this stressed-comfort-food group.

Another study supports this finding, reporting that stress responses in rats, namely ACTH and corticosterone (i.e., the rat analogue to cortisol) responses and corticotropin-releasing factor (CRF) mRNA, were reduced by ingestion of palatable foods (Foster, et al., 2009). Another study reported that during stress, mice increased the percent of calories obtained from a high fat diet (Teegarden & Bale, 2008). Further, with restricted high fat access, stress-sensitive (i.e., CRF receptor 2 knockout) mice increased (binge-like) fat consumption. One study looked specifically at rats' eating behavior following a stressor, finding that rats given a choice of food ate diets composed 50-60% of calories from lard (la Fleur, et al., 2005). Authors also reported that consumption seemed to dampen the HPA axis response to the stressor.

Although many studies seem to report that fat and sugar consumption increase with stress exposure, the literature seems to be somewhat unclear regarding whether

overall caloric intake increases or decreases. In the former study above, all stressed mice and particularly genetically stress-sensitive mouse models gained less weight including less weight in fat over the course of the study than controls (Teegarden & Bale, 2008). Interestingly, authors reported that, regardless of weight, stress-sensitive mice with access to 'comfort food' exhibited an increase in abdominal fat. The finding of increased abdominal fat following a stressor finding was corroborated by the latter study above, which found that abdominal fat increased in all stressed groups, although this study did not include a non-stressed control group (la Fleur, et al., 2005). This latter study reported that rats exposed to a stressor and given a choice of greater lard in their diet, consumed greater amounts of lard, and yet exhibited a greater decrease in total caloric intake over time. Notably, they still gained as much weight and abdominal fat as rats not given a choice. In another study above, all stressed rats decreased caloric intake and gained the least amount of weight (Pecoraro, et al., 2004).

Not all studies agree with the role of the HPA axis in decreasing caloric intake. One classic article, for example found that increasing concentrations of circulating glucocorticoids increase the incentive salience of calories (Berridge & Robinson, 1998). Moreover, failure to gain weight in the stress condition may be the result of several factors. It may be a result of the type of stressors used, which may have increased physical activity among stressed mice. Alternatively, it may be that different murine strains metabolize fat and sugar differently. One study on metabolism in murine models of obesity found that one type of obesity-prone mouse gained excess weight based particularly upon the amount of calories from fat (Petro, et al., 2004). This finding

suggests that differences in the metabolism of fat may be partially responsible for different body weight increases irrespective of overall calorie intake.

3.2 Human Studies

In human studies, positive, negative, and mixed results were reported. Firstly, some studies demonstrate increased consumption with increased stress. In 68 healthy men and women, stressed emotional eaters ate more sweet high-fat foods and a more energy-dense meal than unstressed and non-emotional eaters (Oliver, et al., 2000). One study of 169 undergraduate male and female students found that not only do a percentage claim to eat more when stressed (46% of women, 17% of men), but those women who eat more tend to eat more fatty, sweet foods (Zellner, et al., 2006). A study of 59 healthy pre-menopausal women found that greater negative mood in response to a stressor was related to greater food consumption (Epel, et al., 2001). Among 131 medical students, 36% self-described stress-eaters tended to gain more weight during exam periods (Epel, et al., 2004). In another study, job stress was associated with greater food intake, particularly in terms of saturated fat and sugar (Wardle, et al., 2000). Thus, these studies support the hypothesis that some individuals when stressed will consume greater sweet and fatty foods and greater food in general, which causes them to gain weight.

On the other hand, some studies report mixed or negative findings regarding a relationship between stress and energy consumption. Moreover, a number of important moderators are proposed that may affect this relationship. One study found that sadness, evoked from viewing distressful movie clips, decreased while positive emotion

increased chocolate intake among a group of men, suggesting that changes in eating behavior are relatively specific to types of stress (Macht, et al., 2002).

Indeed, one review of stress effects on eating in animal models reported that acute stressors may act differently than chronic stressors to induce different eating behaviors (Ellacott, Morton, Woods, Tso, & Schwartz, 2010). As described above, some stressors may be associated with increased weight and others with decreased weight. For example, one study found that variety of food choices predicted weight loss and weight loss maintenance among overweight individuals (Raynor, et al., 2005). Increased food variety was thought to perhaps induce a more stressful eating experience, particularly around high-calorie foods. Thus, it may be that the precise type of stress is integral to predicting the valence of the eating response (e.g., increase, decrease, no change).

Moreover, it is likely that stress-related food intake only occurs in a subgroup of obese individuals. An experimental study of 22 obese subjects found that the subgroup of binge-eating participants exhibited increased HPA responses (e.g., blood cortisol), stress-related hunger and desire-to-binge-eat ratings following a stressor, suggesting that even among obese individuals a subgroup of stress-related binge-eaters may exist (Gluck, et al., 2004). Another study found that by experimentally increasing HPA axis activity, researchers could increase food consumption (George, et al., 2010).

To summarize, these studies suggest that not all obese individuals gain weight through the same mechanism, and stress is not always associated with increased food intake. Indeed, in lab stress protocols, some decrease intake and some do neither (Dallman, 2010). However, a growing literature suggests that for some individuals, a

variety of stressors are associated with increased food consumption (O'Connor, Jones, Conner, McMillan, & Ferguson, 2008; Oliver, et al., 2000; Wardle, et al., 2000). One recent study hints at a mechanism through increases in HPA axis activation, but few further studies have been conducted (George, et al., 2010).

Since 66% of US adults meet criteria for overweight (BMI \geq 25) or obesity (BMI \geq 30; Agurs-Collins & Bouchard, 2008) in the US and only about 40% are thought to increase eating behavior in response to stress, it seems likely that a stress-eating subgroup exists. But since it appears that obesity is a complex disease with no one unique etiology, it seems likely that this stress-sensitive subgroup represents one of several ways in which individuals develop obesity.

A positive feature of this literature is that studies are largely experimental and consist of both human and animal samples. However, the available evidence has a number of weaknesses. The studies tend to use small samples, some of which draw entirely from particular samples (e.g., medical students, binge-eating subjects) or clinical populations. Thus it is unclear whether conclusions can be extended to the general population. Moreover, it seems unclear whether the stress-related food consumption is specific to sweet or fatty foods, energy-dense foods, or overall caloric intake. And, the human and animal studies reviewed above seem to give conflicting evidence regarding whether individuals increase or decrease total calorie intake in response to stress or whether individuals increase or decrease weight.

To summarize, despite its shortcomings, animal and human literature does seem to suggest that stress appears to be associated with increased food intake in some individuals, but evidence is mixed on how or why this occurs. Some studies hint that

only fatty and sweet food (i.e., 'comfort food') consumption increases among this group, whereas other studies suggest that overall energy intake is increased. Moreover, the specific type of stress that elicits increased consumption has not been identified. Therefore, studies are needed to explore in more detail the mechanism by which stress may increase food consumption and thus lead to obesity.

Future investigations are needed to parse out the different types of stress-eaters as well as the different eating behaviors induced by various types of stress. It is possible that the path towards understanding this relationship lies in genetic vulnerabilities that predispose some to drastically alter eating behavior in response to stress. One possible source of genetic vulnerability will be discussed in greater detail below.

4. Genetic Effects on Obesity

Before exploring which pathways are appropriate avenues for research hypotheses, one must first consider the genetics of obesity. Although up to now this document has focused on environmental predictors of obesity, studies show that interindividual, genetic differences in predispositions to obesity are substantial. Since early adoption studies by Stunkard and colleagues, family resemblance in obesity traits has been shown to be strongly genetically influenced (Haberstick, et al., 2010).

In one example, when researchers forced standardized overfeeding, they found large individual differences in weight gain and greater similarity among twins (Bouchard, et al., 1990). Even when researchers implemented exercise training programs with young and healthy adult volunteers, they found substantial individual differences in training-induced physiological changes, with the range between low and high responders reaching several fold (Rankinen & Bouchard, 2008). These findings suggest a genetic predisposition for both the storage of calories as body weight and for the benefit of exercise.

Exploring the biological origins of obesity, scientists have been publishing an increasing number of studies on obesogenic genes. Although the latest update of a gene map for obesity-related phenotypes reported >600 loci, the majority are only based on a single positive study (Rankinen & Bouchard, 2008). Obesity gene association studies have focused primarily on 127 candidate genes that have emerged from genome-wide association studies (GWAS; Andreasen & Andersen, 2009; Bouchard, 2008; Qi & Cho, 2008). Of these, 23 have been supported in at least five positive studies and 12 have been

supported in 10 or more studies (Bray, 2008). Sixteen of these have putative effects on BMI-defined obesity (Andreasen & Andersen, 2009).

Three basic classes of genes regulate energy homeostasis. These classes include *energy expenditure*, *partitioning*, and *energy intake* (Chung & Leibel, 2008). Among other roles, *energy expenditure* genes determine the efficiency of physical activity to burn calories and the incentive for an individual to engage in physical activity. *Partitioning* genes include those that determine the capacity or proclivity to store calories as fat, protein, or carbohydrates. *Energy intake* genes include those that regulate food intake, hedonic reward incentives, and executive control over food intake decisions.

Among these classes, genes regulating *energy intake* may be particularly promising and understudied research targets. Dysregulation of certain neurotransmitter systems has been suggested as a primary mechanism by which humans and animals gain excess weight. Since dopaminergic circuits are particularly integrated within the human gustatory and appetitive feedback mechanisms, certain functional polymorphisms of dopaminergic genes may be instrumental in predicting overweight phenotypes.

Despite the importance of hedonic and reward-related feedback of eating behavior, comparatively little obesity research has targeted dopamine (DA). One reason may be that DA gene SNPs have not emerged as primary determinants of obesity phenotypes in the GWAS literature (Bouchard, 2008; Lenard & Berthoud, 2008). However, the lack of a single gene main effect does not necessarily obviate its importance if it is only when interacting with environmental factors that a gene significantly predicts body weight (Bogardus, 2009). As described later in more detail,

the same genotype can have opposite effects on the obesity phenotype under different environmental exposures. If not included within the analyses, the presence of certain key environmental exposures may obscure the predictive importance of particular genes.

5. DRD2 as a Genetic Determinant of Obesity

Next, evidence highlighting the role of the receptor in weight regulation will be reviewed. Incorporating studies found in **Table 3**, the next section will show that since DRD2 is 1) an energy-intake-related gene, 2) is responsive to stress effects on calorie consumption, and 3) appears to influence behavioral (e.g., eating behavior) mechanisms involved in obesity, it may be an ideal candidate gene to explore how stress by gene interactions might help predict obesity.

Table 3: Selection of Animal and Human Studies on the Role of DRD2 in Obesity

Authors	Sample Size	Predictor Variables	Outcome Variables	Findings
<i>ANIMAL STUDIES</i>				
(Orosco, Rouch, & Nicolaidis, 1996)	Obese and lean Zucker rats	Fasting and eating schedules	DRD2 receptor availability, HPA axis activity	Obese Zucker rats have fewer DRD2 receptors and reduced hypothalamic DA activity when fasting, but release more DA when eating. They also do not stop eating in response to cues that stop eating in lean Zucker rats.
(Bina & Cincotta, 2000)	Female, obese (ob/ob) and lean (C57BL/6J) mice	Treatment with DRD2 agonist bromocriptine vs. no treatment	Body weight and blood glucose	Increasing central DA tone through DRD2 agonists eliminates overeating and hyperglycemia.
(Kruchenko, 2009)	Hypertensive (SHR line) rats	Stress condition and DRD2 antagonist drug condition	Eating behaviors, neurological signaling.	D2-receptors antagonist (sulpyride) resumes stress-injured activity and increases food motivation.
(Diaz-Torga, et al., 2002)	DRD2 knockout	KO condition	Body weight	Body weights were similar at birth, but DRD2 KO mice

	(KO, B6.129S2-DRD2) and wild-type mice			developed less body weight and adipose tissue despite similar food intake between groups.
HUMAN STUDIES				
(Jenkinson, et al., 2000)	Pima Native Americans	DRD2 genotype	BMI	Modest association between DRD2 mutation and BMI.
(Stice, Spoor, Bohon, & Small, 2008)	2 studies (1. 43 young adult females, 2. 33 adolescent girls)	Genotype group (DRD2 Taq1A allele) & Study group stimuli. 1. Food visual and taste stimulus, 2. Visual shape stimulus	Striatal activation	Striatal activation in response to food intake is related to current and future increases in body mass and these relations are moderated by the presence of the A1 allele of the Taq1A.
(Stice, Yokum, Bohon, Marti, & Smolen, 2010)	44 adolescent female high school students ranging from lean to obese	Study group brain activation response to stimuli 1. Food visual and taste stimulus, 2. Visual shape stimulus	Future BMI	Weaker brain activation in response to imagined intake of palatable foods, versus imagined intake of unpalatable foods or water, predicted future increases in BMI for those with the DRD2 Taq1A allele.
(van Strien, Snoek, van der Zwaluw, & Engels, 2010)	In prospective 4y study of 279 adolescents	DRD2 Taq1A genotype and stressful parental rearing	Questionn. measures of emotional eating	The Taq1A SNP was associated with emotional eating among those with stressful rearing.
(Volkow, et al., 2003)	10 healthy non-obese subjects	Restraint, Emotionality & Externality measured	PET-measured baseline DRD2 receptors	Emotionality negatively correlated with baseline DRD2 receptors in dorsal striatum (higher emotionality, lower D2

	by the Dutch Eating Behavior Questionnaire (DEBQ). Food stimulation condition.	and changes in extracellular DA to food stimulation.	receptors), whereas externality was not.
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5.1 Dopamine and Obesity

Dopamine function appears to be integral to the development of some types of obesity. Given the versatility of experimental models, animal studies have been particularly informative. In one study, obesity-prone rats had 50% reduction in basal extracellular DA in the nucleus accumbens (NA), dorsal striatum, and medial prefrontal cortex (Geiger, et al., 2008).

Previous studies in rodents have also shown increased DA release and turnover in response to acute feeding (Hernandez & Hoebel, 1988; Yoshida, et al., 1992) as well as 33% decreased basal levels of DA in response to chronic food deprivation (Pothos, Hernandez, & Hoebel, 1995). Obese male Sprague-Dawley rats have reduced DA turnover in the hypothalamus compared to a diet-resistant strain (Levin & Dunn-Meynell, 1997) and become obese only when given access to a palatable, energy-dense diet (Levin & Dunn-Meynell, 2002). From these studies, one learns that obesity in rodents seems to reduce DA transmission in certain brain areas such that their brains seem to mimic those of rodents who are chronically food deprived.

Human studies appear to corroborate animal findings linking DA to obesity. BMI was found to be the best negative predictor of striatal DA transporter availability (P. S.

Chen, et al., 2008). Another study found a negative correlation between BMI and fMRI responses to gastric distention in dopaminergic (midbrain, hypothalamus, amygdala, thalamus) brain regions consistent with disruption of dopaminergic signaling in obesity (Tomasi, et al., 2009).

One review found that individuals with attention-deficit-hyperactivity disorder (ADHD), a disorder with a well-known dysfunctional dopaminergic etiology, have higher-than-average BMI and/or a higher prevalence of obesity compared to controls (Cortese & Morcillo Penalver, 2010). The study suggests that both ADHD and obese populations present with behaviors consistent with a 'reward-deficiency syndrome.' Like in animal research, it seems that a dysfunction in DA transmission may underlie obesity, particularly a DA hypofunction associated with reward deficiency.

Taken together, these studies suggest that attenuated central DA activity may reduce the reinforcement associated with eating and may in turn induce compensatory increased eating behavior, leading to obesity. It is possible that palatable, energy-dense foods are particularly instrumental in the development of obesity in some individuals.

The literature also includes a number of negative and mixed findings. For example, obese rats release more DA during eating than normals (Yang & Meguid, 1995). Of course, it is possible that this finding does not directly contradict the above findings if obese rats require greater DA release to achieve reinforcement due to a downregulation of DA receptors. This process is discussed below. Also, it is unclear whether hyper-responsivity of dopaminergic circuitry increases risk for future weight gain or is a result of conditioning from overeating palatable foods (Stice, et al., 2010). If

the latter were true, then DA brain abnormalities would not necessarily underlie a reward-deficiency problem among obese individuals.

5.2 DRD2 and Obesity Overview

Although helpful in understanding the basic circuitry involved in overeating, altered DA levels may in fact signal an up- or down- regulation of DA receptors, which tend to be the drivers of more chronic changes overall in DA metabolism. Studies have shown, for example, that a chronic change in DA receptor expression is a prerequisite for behavioral sensitization (Kuczenski & Segal, 1999). As described below, down-regulation of DA receptors (e.g., particularly DRD2) may be at the heart for overeating in obese rats and possibly humans.

Animal studies have been particularly useful in understanding the role of DRD2 receptor activity in obesity. For example, obese Zucker rats have fewer DRD2 receptors and reduced hypothalamic DA activity when fasting but release more DA when eating and do not stop eating in response to cues that stop eating in lean Zucker rats (Orosco, et al., 1996). Moreover, increasing central DA tone through DRD2 agonists eliminates hyperphagia or overeating (Bina & Cincotta, 2000).

In the Pima Indian population, a missense substitution in the DRD2 gene has been associated with resting energy expenditure (Tataranni, et al., 2001), greater BMI and type II diabetes (Jenkinson, et al., 2000). Several population studies have documented an association between reduced DRD2 expression (viz. Taq1A allele) and obesity (Comings, et al., 1993; Comings, Gade, MacMurray, Muhleman, & Peters, 1996; Noble, et al., 1994). Low DRD2 receptor availability, shown to be associated with the A1

allele of the of RS1800497 SNP (Ritchie & Noble, 2003), is thought to make individuals less sensitive to reinforcement such that they may seek more powerful reinforcers to overcome their lack of DA. This may increase their risk for obesity and other addictive activities associated with DA transmission.

Despite the seemingly convincing findings, contradictory findings are reported. For example, even in positive population studies, the most studied vulnerability DRD2 SNP is only found in 50% of obese individuals compared with 30% of lean individuals according to a review (Epstein, Leddy, Temple, & Faith, 2007). In one Nauran and Australian sample, the Taq1A allele did not correlate with BMI at all (Southon, et al., 2003). In another study, the effect is moderated by gender such that female smokers carrying the A1 allele had lower BMI, whereas male carriers had greater BMI than other groups (Noble, et al., 1997) . In others, the A1 allele was associated with an obesity phenotype but not with cardiovascular risk factors of interest including cholesterol and triglycerides (Noble, et al., 1994). In a recent study, the A1 allele was associated with obesity in a Mexican-American sample (Duran-Gonzalez, et al., 2011).

Also, it is unclear if low DRD2 availability is responsible for overeating in obese subjects or controls as well. As described above, a DRD2 receptor blockade causes obese not lean rats to overeat, but other studies have found effect in non-obese as well (Fetissov, Meguid, Sato, & Zhang, 2002; Orosco, Gerozissis, Rouch, Meile, & Nicolaidis, 1995). Thus, the precise mechanism of DRD2 in the development of eating behavior is still unclear.

5.3 DRD2 Associated with Behavioral Mediators of Obesity

Despite these mixed findings, DRD2 may be the most appropriate gene for GxE studies predicting obesity given its association with a likely mediator of obesity, eating behavior. Most recently, researchers have been extending scholarship on behavioral mediators to receptor regulation, finding that repeated intake of sweet and fatty foods results in downregulation of DRD2 receptors, increased binding, and decreased DRD2 sensitivity (Bello, Lucas, & Hajnal, 2002; Colantuoni, et al., 2001). In fact, the Ta1A polymorphism was implicated as part of a multiSNP locus associated with ventral striatum reactivity (Nikolova, Ferrell, Manuck, & Hariri, 2011)

Striatal activation in response to food intake is related to current and future increases in body mass, and these relations are moderated by the presence of the A1 allele of the Taq1A polymorphism (Stice, et al., 2008; Stice, et al., 2010). In this latter study, reward activity in response to food was helpful in predicting future weight gain, but only when moderated by DRD2 genotype. This suggests that only the interaction between environmental exposure and genotype was sufficient to describe brain activation. Several GxE studies in DRD2 propose a model by which intake of substances and food or exposure to stress leads to DRD2 sensitivity and then promote compulsive or addictive behaviors.

This line of research is supported by a more developed literature on the role of DRD2 in addictions and compulsive behaviors. It is known that DRD2 receptors in the striatum play a key role in the development of addiction to natural rewards (Volkow, Wang, Fowler, & Telang, 2008). Low availability of D2 receptors predisposes to the development of compulsive behavior as well (Nader, Czoty, Gould, & Riddick, 2008;

Volkow, et al., 2008). Compulsive behavior can also be linked with addictive behaviors such as in one study where the link between coping motives and chronic alcohol outcomes was moderated by the Taq1A allele (van der Zwaluw, Kuntsche, & Engels, 2011). In another study, the A1 allele was associated with pack years smoked (Verde, et al., 2011).

Although Taq1A is often the subject of DRD2 studies, several other polymorphisms are being investigated, although they are found primarily in addictions studies at this point. Several DRD2-related polymorphisms including Taq1B and intron 6 sites are strongly associated with alcoholism (Noble, Zhang, Ritchie, & Sparkes, 2000). The RS1116313 is a tagging SNP that can act as a proxy for a large number of other SNPs. Despite its usefulness, few studies have explored its role in complex diseases or psychiatric disorders. One found a relationship between RS1116313 and alcoholism (Bhaskar, Thangaraj, Non, Singh, & Rao, 2010). This study was followed by a subsequent study that found an association between this SNP and alcoholic 'craving,' DSM-IV criteria alcohol dependence, and dependence without craving (all p 's < 0.001; Agrawal, et al., 2012). However, another study found no association between habitual smoking or drinking and this SNP (Liu, et al., 2005).

Although relatively few studies have been conducted on the RS1076560 polymorphism, it remains an interesting object of research in addictions and may be an interesting target for obesity research. Drug users carried more frequently the minor allele of DRD2 polymorphism RS1076560G > T SNP and the RS1800497 SNP, with similar tendencies for a number of other SNPs (Doehring, et al., 2009). The same RS1076560 allele was linked to substance addiction in smokers (Morton, et al., 2006). The

SNP was also linked to cocaine abuse primarily in Caucasians (Moyer, et al., 2011) and to greater striatal dopamine signaling and motoric coordination (Fazio, et al., 2011).

The RS1076560G > T change in intron 6 seems to affect splicing, leading to a shift in the balance between D2 receptor isoforms DRD2L (long) and DRD2S (short) (Picetti, et al., 1997). In vivo, these two isoforms functionally oppose each other, favoring DRD2L (Moyer, et al., 2011; Usiello, et al., 2000). Perhaps through these mechanisms, the RS1076560 SNP has been found to affect D2 receptor availability and signal transduction in the dopaminergic pathways (Lucht, et al., 2010).

The documented role of DRD2 in addictions is indicative that the DRD2 receptor may mediate a powerful reinforcing response, perhaps through modulating receptor availability and dopaminergic signaling. It is through the reinforcing aspects of eating, particularly those aspects found to increase as a reaction to stress, that may predict obesity in a subset of individuals depending upon DRD2 genotype.

5.4 Stress as Moderator of DRD2 Activity

Despite a variety of published studies demonstrating a link between DRD2 availability and addiction, more recent studies have found that stress may be an environmental moderator of its effect on various behaviors. Although the Taq1A allele had been associated with alcoholism in meta-analysis (Noble, 2000), about half of published DRD2/alcohol addiction association studies reported negative findings (Madrid, MacMurray, Lee, Anderson, & Comings, 2001). It was later demonstrated that stress moderates the relationship between Taq1A and alcoholism in a sample of 309

adult males 18-87 years old (Madrid, et al., 2001). In this sample, the A1 allele was associated with alcoholism, but only when participants reported high stress levels.

Another landmark study found that only in boys with the A1 allele, the family stress score was negatively associated with visuospatial function and P300 amplitude and latency. These findings suggested that the relationship between DRD2 and cognitive function was moderated by family stress (Berman & Noble, 1997). It is possible that poor cognitive function is a mediator of poor dietary choices, which thereby promote obesogenic behaviors.

Although not specifically focused on stress-mediated effects, some studies have looked at links between emotion, mental processing, and decision making. One study looking at the RS1076560 allele found greater amygdala activity during implicit processing and greater dorsolateral prefrontal cortex (DLPFC) response during explicit processing of facial emotional stimuli in G/G subjects compared with G/T, indicating a role for the polymorphism in processing of emotional information (Blasi, et al., 2009). This same allele was found to predict poor negative learning or avoidance of negative consequences in humans (Frank & Hutchison, 2009). Thus, stress appears to moderate the reward effects of DRD2 in some cases, perhaps through changes in mental processing or poor learning from negative consequences.

Stress also appears to moderate the effect of DRD2 on eating behavior directly; although, both animal and human literatures are very much in their early stages. Only one animal study could be located. It found that antagonism of DRD2 receptors reinstates stress-injured behavior and increases eating in mice (Kruchenko, 2009). Only a few human studies were located. In one prospective 4-year study of 279 adolescents, the

Taq1A was only associated with emotional eating among those with stressful rearing or over-controlling parenting (van Strien, et al., 2010).

In other study, the tendency to eat in response to negative emotions (e.g., perhaps when stressed) was correlated with fewer DRD2 receptors in the dorsal striatum. This relationship would be expected if, as hypothesized above, a lack of DRD2 receptors was associated with lower reinforcement from eating behavior. Therefore those with less receptors would be required to seek greater reinforcement, leading to obesity.

Very few negative studies were found on the relationship between stress and DRD2 beyond the more general studies described above that failed to find an association between DRD2 and obesity or eating. This may be the result of limited literature on the topic overall. Although no study has conclusively shown dopamine to exert control over ACTH, an important stress-related hormone (de Bruin, Feelders, Lamberts, & Hofland, 2009), it is known that the intermediate lobe in the pituitary is under tonic inhibitory control of the hypothalamic dopaminergic neurons (Saiardi & Borrelli, 1998), further highlighting positive links between stress and DA transmission.

In summary, despite some mixed findings, a small number of animal and human studies have found that DA and particularly DRD2 gene expression may be associated with not only obesity but also stress-reactive addictive behaviors (e.g., eating behavior) that are thought to mediate the development of obesity. Moreover, a variety of DRD2 polymorphisms are associated with substance-related addictive behavior. These same polymorphisms may also be associated with the type of reinforcing eating behavior suspected to mediate the development of obesity.

6. GxE Interactions in Obesity

As the preceding review has suggested, it is only through a combination of genetic and environmental factors that one can begin to understand obesity and eating behaviors that may mediate its development. Traditional approaches have failed up to the preset. For example, Stunkard and colleagues found that family resemblance in obesity traits is genetically influenced (Haberstick, et al., 2010).

But genes alone cannot account for the tripling in obesity prevalence in the last decade (Tamashiro, et al., 2009), widely divergent body weights of genetically similar ethnic groups who eat different diets (Wing, et al., 2001), or a considerable amount of variance in predicting obesity. Even the most promising genetic polymorphisms such as FTO only explain about 1% of the variance in BMI (Frayling, et al., 2007). Finally, many failures to replicate (e.g., >600 loci, mostly based on a single positive finding) gene main effects may be due to moderation of gene effects by stress (Rankinen & Bouchard, 2008), although it is still unclear how stress might account for the difference in explanatory power.

The success of previous GxE studies in helping us understand complex diseases suggests that further study of how stress affects dopaminergic transmission in the development of unhealthy excess body weight may be warranted. In one of these studies, an interaction between APOE genotype and caregiver status predicted triglycerides (Kring, et al., 2010). In this study, stressed caregivers with the TT genotype experienced higher triglycerides, but controls with the same TT genotype experienced reduced triglycerides.

Studies have also revealed that the 5-HTTLPR polymorphism of the serotonin transporter gene moderates the effect of stressful life events on development of depression (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010). In either case, without having both genotype and environmental stress measures, the interaction would have been missed. The following section will describe the current research project, which aims to explore a GxE interaction between DRD2 and stress exposure predicting obesity that is mediated through an increase in eating behaviors.

7. Dissertation Methodology

In the following section, a model (see **Figure 1**) is proposed whereby stress exposure promotes obesogenic behavioral components among a genetically defined subset of individuals. Behavioral (e.g., increased calorie consumption) changes may be particularly significant among those with sensitive reward system circuitry, operationalized as those with sensitive D2 receptor circuitry.

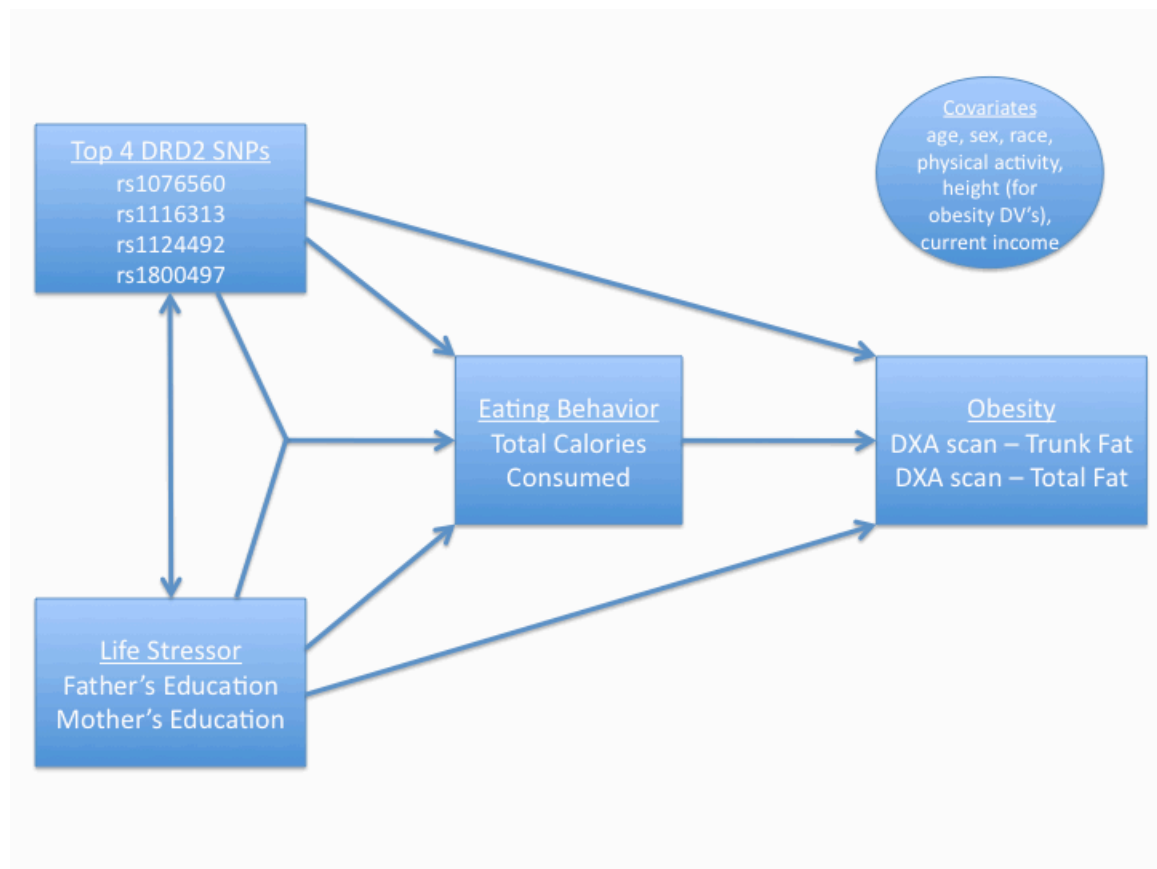


Figure 1: Mediation Model - Gene x Environment Interaction Predicting Obesity, Mediated by Eating Behavior

7.1 Study Design and Sample

Subjects were recruited to take part in the Family Heart Study, a single center investigation designed to examine the relationship between psychosocial behaviors and cardiovascular risk factors. The sample was recruited between August 2004 and September 2008, and was comprised of 542 volunteers without cardiovascular disease. The study was conducted at Duke University Medical Center, and all subjects gave informed consent prior to their participation using a form approved by the Duke University Medical Center Institutional Review Board. Men and women between the ages of 18 and 55 years were selected for inclusion. Sibling pairs were recruited via community based advertisements. Exclusions included pregnancy, diabetes, hypertension that required medication, the use of psychoactive medications, anti-inflammatory agents including non-steroidal anti-inflammatory drugs, and use of aspirin. All subjects were required to read and write English. Descriptive statistics of this sample are summarized below in Table 8.

7.2 Variables

7.2.1 Environmental Predictors

I incorporated two classes of predictor variables representing the environmental and the genetic predictors of eating behavior. Apart from the literature reviewed above, childhood SES is chosen as a stress-related variable for a number of reasons. Parents' education or occupation, which is partially determined by one's education, is a common

measure of childhood socioeconomic status as seen in several meta-analyses (Gonzalez, et al., 2009; Tamayo, et al., 2010). As mentioned above, it is hoped that the current study will be replicated in a larger sample, and childhood socioeconomic status is a common variable available in multiple large datasets. Parental education has been associated with changes in eating and obesity among both men and women, and as a variable it is perhaps a more objective measure of stress than ‘perceived stress,’ for example.

It is hypothesized specifically that childhood SES indexed by low parental education will interact with DRD2 variants to predict obesity indices and eating behavior; but, given the potential important impact of other stress indicators, other indices of stress (e.g., SES, perceived stress scale score, etc.) will be explored to see if they also interact with DRD2 to affect dependent variables. Specific methods are detailed below.

7.2.2 Genetic Predictors

For genetic predisposition, a number of SNPs in the DRD2 gene will be investigated. As described above, the DRD2 gene has not only been associated with a predisposition to obesity in a number of association studies, but it has also been associated with increased compulsive addictive behavior including eating behavior, particularly in response to stress.

Despite many strong links between DRD2 and reinforcement from eating, few studies have examined this relationship and even fewer have examined DRD2xE interactions affecting eating behavior and obesity. Since the study is conducted in the Behavioral Medicine Research Center’s most recently funded program project grant

(PPG), it is restricted to the DRD2 polymorphisms that have been genotyped in that dataset. Additionally, considerable evidence summarized above supports the Taq1A allele's association with a number of stress-related addictive and obesity-related variables; therefore its associated SNP (i.e., RS1800497) will be included in this study.

Alternatively, very few additional polymorphisms have been demonstrated as related to relevant phenotypes or behaviors. Therefore, a more method-driven process will be used to identify SNPs for evaluation in this research project. In an attempt to both control for multiple tests and limit the scope of this project, a National Institute of Health (NIH) SNP tagging program was used <http://snpinfo.niehs.nih.gov/snptag.htm>.

As shown in Table 4, two populations that best represent the PPG sample were chosen. SNPs present in the provided dataset were then forced-in, and DRD2 SNPs not present in the dataset were forced-out. SNPs that are forced-out are only forced out of the final output list of tagging SNPs; these SNPs are still part of the lists of captured SNPs used to identify tagging SNPs.

Table 4: List of DRD2 Tagging SNPs, Distribution Statistics, and SNPs Captured

TagSNP	rs1076560	rs2471857	rs1125393	rs1079595	rs2075654	rs1125394	rs2283265	rs1116313	rs1076563	rs1107162	rs2587548	rs12800853
Size	22	22	22	20	20	20	20	19	19	16	16	16
ave.MAF	0.1445	0.1537	0.1435	0.1467	0.1467	0.1467	0.1467	0.3354	0.3354	0.3517	0.3517	0.3517
ave.r2	0.9135	0.9168	0.9168	0.9453	0.9453	0.9166	0.9559	0.9556	0.961	0.9461	0.967	0.9651
SNPs.captured	rs1076560	rs1076560	rs1076560	rs1076560	rs1076560	rs1076560	rs1076560	rs1076563	rs1076563	rs1076563	rs1076563	rs1076563
	rs1079727	rs1079594	rs1079594	rs1079594	rs1079594	rs1079594	rs1079594	rs1116313	rs1116313	rs1107162	rs1107162	rs1107162
	rs1079594	rs1079595	rs1079595	rs1079595	rs1079595	rs1079595	rs1079595	rs1107162	rs1107162	rs1116313	rs1116313	rs1116313
	rs1079595	rs1079596	rs1079596	rs1079596	rs1079596	rs1079596	rs1079596	rs12363125	rs12363125	rs12363125	rs12363125	rs12363125
	rs1079596	rs1079597	rs1079597	rs1079597	rs1079597	rs1079597	rs1079597	rs12364051	rs12364051	rs12364051	rs12364051	rs12364051
	rs1079597	rs1079727	rs1079727	rs1079727	rs1079727	rs1079727	rs1079727	rs12800853	rs12800853	rs12800853	rs12800853	rs12800853
	rs11214607	rs11214607	rs11214607	rs11214607	rs11214607	rs11214607	rs11214607	rs2587548	rs2587548	rs2587548	rs2587548	rs2587548
	rs1124491	rs1124491	rs1124491	rs1124491	rs1124491	rs1124491	rs1124491	rs2734831	rs2734831	rs2734831	rs2734831	rs2734831
	rs1125393	rs1125393	rs1125393	rs1125393	rs1125393	rs1125393	rs1125393	rs2734833	rs2734833	rs2734833	rs2734833	rs2734833
	rs1125394	rs1125394	rs1125394	rs1125394	rs1125394	rs1125394	rs1125394	rs2734837	rs2734837	rs2734837	rs2734837	rs2734837
	rs2075654	rs2075654	rs2075654	rs2075654	rs2075654	rs2075654	rs2075654	rs2734838	rs2734838	rs2734838	rs2734838	rs2734838
	rs2283265	rs2283265	rs2283265	rs2283265	rs2283265	rs2283265	rs2283265	rs2734839	rs2734839	rs2734839	rs2734839	rs2734839
	rs2471851	rs2471851	rs2471851	rs2471851	rs2471851	rs2471851	rs2471851	rs4587762	rs4587762	rs4587762	rs4587762	rs4587762
	rs2471854	rs2471854	rs2471854	rs2471854	rs2471854	rs2471854	rs2471854	rs4938017	rs4938017	rs4938017	rs4938017	rs4938017
	rs2471857	rs2471857	rs2471857	rs2471857	rs2471857	rs2471857	rs2471857	rs7122246	rs7122246	rs7122246	rs7122246	rs7122246
	rs2734836	rs2734836	rs2734836	rs2734836	rs2734836	rs2734836	rs2734836	rs7131440	rs7131440	rs7131440	rs7131440	rs7131440
	rs4648319	rs4648319	rs4648319	rs4648319	rs4648319	rs4648319	rs4648319					
	rs6278	rs6278	rs6278	rs6278	rs6278	rs6278	rs6278	1116313=510				
	rs7103679	rs7103679	rs7103679	rs7103679	rs7103679	rs7103679	rs7103679					
	rs7350522	rs7350522	rs7350522	rs7350522	rs7350522	rs7350522	rs7350522					
	RS1076560=508											

TagSNP	rs2002453	rs4581480	rs4938019	rs6275	rs1124492	rs1124493	rs4274224	rs4586205	rs6279	rs4350392	rs17601612	rs17529477	rs7131056	rs6277
Size	10	9	9	7	7	7	6	6	5	5	3	2	2	1
ave.MAF	0.2995	0.2453	0.1244	0.3553	0.2583	0.3553	0.4532	0.2202	0.3178	0.1332	0.3873	0.2385	0.39	0.466
ave.r2	0.94	0.8972	0.8621	0.9773	0.8564	0.9773	0.9482	0.9071	0.9843	0.8234	0.8908	1	1	1
SNPs.captured	rs1076562	rs4581480	rs10891551	rs1124493	rs1124492	rs1124493	rs4274224	rs1076562	rs1124493	rs10891551	rs11601054	rs17529477	rs7131056	rs6277
	rs1124492	rs4936270	rs11214611	rs6275	rs2002453	rs6275	rs4936271	rs2002453	rs2734841	rs4350392	rs17601612			
	rs2002453	rs4936274	rs4350392	rs2734841	rs2245805	rs2734841	rs4245146	rs2005313	rs6275	rs4648317	rs4630328			
	rs2245805	rs11214613	rs4648317	rs6276	rs17115583	rs6275	rs4245147	rs2245805	rs6276	rs4938019		RS17529477=511		RS6277=510
	rs2005313	rs4245148	rs4938019	rs6279	rs4436578	rs6276		rs4586205	rs6279	rs7122454			RS7131056=509	
	rs4586205	rs4460839			rs4620755	rs6279		rs4648318			RS17601612=512			
	rs4648318													
		RS4938019=510					RS4274224=511							
		RS4581480=511		RS6275=512		RS1124492=500?		RS4586205=510						

Note. SNPs found in more than one “SNPs captured” list are color-coded in same shade. SNPs found in only one list are colored black. Tagging SNPs with >500 participants genotyped are marked at bottom of column.

Knowing that the SNPs in the PPG study were purposefully tagged given their distribution as haplotype markers, haplotype blocks were then sought within the lists of SNPs associated with each tagging SNP. Three tagging SNPs that were proxies for greater than 10 SNPs (i.e., RS1076560, RS1116313, RS1124492) were then chosen. If multiple tagging SNPs captured the same SNPs (i.e., haplotype), then the tagging SNPs for which greater than 500 participants were genotyped were chosen.

One of the three SNPs appeared to tag a haplotype block, although not all captured SNPs were found in the list under each tagging SNP in the block. In this case, a SNP was chosen that captured not only two other tagging SNPs, but also a number of SNPs unique to the tagging SNP (i.e., RS1124492). Those top 3 DRD2 SNPs output by the program that represent the greatest area (i.e., serve as proxies for the greatest number of SNPs on the DRD2 gene) as well as the Taq1A SNP (i.e., RS1800497) are used in analyses. All known relevant research findings have been summarized above, except for RS1124492 since no studies have been published to date.

In those DRD2 SNPs for which research has already been conducted, it was expected that those with alleles associated with a stress-sensitive polymorphism or with a low availability of DRD2 receptors would experience greater reinforcement from eating and therefore will increase total calorie consumption. These stress-sensitive polymorphisms would also be associated therefore with increased obesity, mediated by increased calorie consumption in this population. In those SNPs for which no prior research has been conducted, these analyses are exploratory.

7.2.3 Total Calories as Mediator

I expected this GxE interaction to predict obesity through increased eating behavior. Given the research reviewed above it is not yet understood whether increased stress combines with a sensitive DA system (i.e., assessed using DRD2 SNPs) to increase solely calories from fat and sugar or total calories. In this study, one will also look at how the model predicts total calories consumed in a 24-hour diet recall, since it is thought that total calories are more likely than fat or sugar to contribute to weight gain.

Total calories in this study were determined from a 24-hour diet recall using the “Nutrition Data System for Research (NDS-R)” software version 4.02 (Nutrition Coordinating Center, 2000) and collating data from a large database of food items (Schakel, Sievert, & Buzzard, 1988).

7.2.4 Obesity Outcome

As described above, the environmental and genetic independent variables of interest have been associated with both obesity as an endpoint and eating behavior. It is well-known that excess calorie consumption leads to obesity (Bouchard, 2008); however, not all individuals consume excess calories and not all individuals gain weight at the same rate (Bouchard, et al., 1990). The research above seems to be inconsistent about whether those with sensitive reward systems consume greater amounts of ‘comfort foods’ (i.e., foods high in fat and sugar) or total calories.

I hypothesized in this study that the rate of obesity is a function of total calorie consumption rather than fat and sugar consumption. Thus, it was hypothesized that an interaction between both DRD2 genotype and stress exposure would predict obesity

only among those in whom total calories increase. Those who would experience the greatest increase in calorie consumption and thus obesity will be those with low-functioning DRD2 systems combined with high-stress early life experiences.

Among measures of obesity, DXA-scan-measured trunk and total fat have been suggested as the 'gold standards,' given its convenience and yet strong correlation with CT measures of adiposity (Clasey, et al., 1999; Snijder, et al., 2002). As opposed to BMI or waist circumference (WC) which provide indices for adiposity, DXA scans actually measure body fat deposits, even in particular locations in the body (Mazess, Barden, Bisek, & Hanson, 1990).

DXA-scans have demonstrated high accuracy compared to CT, for example, in samples ranging from anorexic to obese participants (Bredella, et al., 2010). DXA scans of trunk and total fat are also very accurate when compared with CT scans (Bertin, Marcus, Ruiz, Eschard, & Leutenegger, 2000; Glickman, Marn, Supiano, & Dengel, 2004). Compared with BMI, DXA scans in one sample were 34.7% and 35.2% more accurate in women and men, respectively (Kennedy, Shea, & Sun, 2009). Another recent study revealed that in a sample of over 9,000 participants, BMI measures misclassified 39% of the sample as non-obese when they were found to be obese by DXA (Shah & Braverman, 2012).

Trunk fat was used as a measure of obesity in this study because it is known, ecologically valid proxy for the harmful effects of obesity. DXA-scan-measured trunk fat offers a strong predictive value for metabolic disturbances, baseline insulin sensitivity, and cardiovascular diseases in multiple ethnicities than overall obesity per se (Lapidus,

et al., 1984; Larsson, et al., 1984; Lundgren, Bengtsson, Blohme, Lapidus, & Sjostrom, 1989; Nelson, Bessesen, & Marshall, 2008; Votruba & Jensen, 2011).

DXA scan-measured total fat mass was also used in the current study given its comparable efficacy at predicting obesity-related risk factors for hypertension, diabetes, and cholesterol in a sample of 12,608 adults (Menke, Muntner, Wildman, Reynolds, & He, 2007). Total fat also predicted additional cardiovascular disease risk factors, including blood pressure and levels of plasma lipids, C-reactive protein, fasting insulin, and glucose in a sample of 8,773 adults (Sun, et al., 2010). In sum, it appears that some disagreement exists among researchers and among clinicians about which measure is the 'gold standard' (Lesser, 2009), however DXA scan-measured trunk and total body fat are certainly valid and appropriate measures .

Recent studies suggest that it is important to adjust trunk and total body fat measurements to whole body proportions (Savgan-Gurol, et al., 2010). In this study, trunk and total body fat were controlled for height, as is common in the literature (Shay, et al., 2011). Research suggests that calculating trunk or body fat without adjusting for body size has been suggested as problematic (Wells, 2007).

7.2.5 Covariates

Apart from the variables stated, the current study controlled for several variables in all models beginning with basic demographic differences such as age, sex and race. Height was controlled in measures of adiposity, as explained. The current study also controlled for physical activity and smoking status, so that body fat measures would not

be biased by metabolic characteristics that might greatly over-or under-estimate the salience of such measures.

Finally in analyses of the effect of childhood SES, current household income was controlled since studies suggest that the predictive ability of stress measures on eating behavior may be ameliorated by a higher current income and worsened by a lower current income (Lidfeldt, Li, Hu, Manson, & Kawachi, 2007). It was also hypothesized that childhood socioeconomic status compared to current socioeconomic status (Braveman, et al., 2005) would have a distinct effect on DRD2 epigenetic processes or genetic vulnerabilities that lead to obesity.

7.3 Procedure

7.3.1 Database Management

Specific procedures were undertaken to clean and recode the dataset. First, 24-hour diet recall data was transformed from 44 worksheet pages of nutrient data with multiple columns for each individual to a single page with one separate line for each participant. The resulting data was then imported into excel, sorted in tandem with the larger PPG dataset and merged into a one collective dataset using SAS software v9.2. All statistical tests in this document utilized version 9.2 of the SAS system for Windows, copyright © 2008. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA

Next, the data was analyzed for incomplete data or multiple entries. About 50 duplicate entries were identified and eliminated using Proc Sort. Then, around 30 slightly altered entries not eliminated utilizing SAS software v9.2 Proc Sort were identified and individually eliminated. Two individuals that had been incorrectly given a repeated 'unique' identifier were identified and given novel unique identifiers.

When descriptive statistics were analyzed, it was discovered that both mother's and father's education included '-1' values that represented a response of "unknown" from participants when asked about their parents' education. These 'unknown' responses were treated as missing data. The resulting parent education data was entered on a 20-point ordinal scale.

7.3.2 Description of Analysis

The data was analyzed according to common GxE statistical methods which have been proposed by researchers Caspi and Moffitt (Caspi, et al., 2010) and used by other GxE researchers such as Koenen (Koenen, et al., 2009). This process involved creating hierarchical, multilevel interactional GxE models, adjusted for covariates, predicting outcomes. Outcome variables (i.e., 24-hour total calories, trunk fat, total fat). Categorical covariates and independent variables including sex, race, leisure physical activity, work physical activity, and DRD2 genotype were dummy coded before being placed in models. Leisure and work physical activity variables were analyzed as categorical variables since the distribution for each was non-linear, including levels such as "not currently working" and "engage in competitive sports."

Given the structure of the dataset, which includes multiple family members, the effect of siblingship/parentage was controlled for. Approximately half of the sample consists of siblings, who are expected to be more alike than non-related others. This was accomplished through multilevel modeling in SAS software using 'Proc Mixed' as the operator, REML as the method of estimation, and variance components (VC) as the covariance matrix. Each model was given a random intercept based on family group identification. Although position in the family (i.e., parent, child) was available as a variable, Age was used instead as a covariate since it provided more variance than position in the family and a continuous measure rather than classification variable to represent age.

The models were constructed in the following order: 1) The equations were controlled for covariates, 2) the main effects of DRD2 SNP alleles on eating behavior (i.e., 24-hour total calorie consumption) and then SES/stress on eating behavior were tested, 3) the effects of the interaction between the four selected DRD2 SNPs and SES/stress on eating behavior were tested, 4) tested the main effects of DRD2 SNPs on obesity (i.e., trunk fat and total fat) and then stress on obesity, 5) the effect of the interaction between DRD2 SNPs and SES/stress on obesity was tested, 6) and finally the main effects and the effect of the GxE interaction on obesity, while controlling for eating behavior, were tested. Note that main effects were added to all models that included higher-order interactions, but these main effects were not explored in-depth unless higher-order interactions were not a better descriptor of the relationships in the data.

7.3.3 Covariate Analysis

To identify the best SES/stress measure, an exploratory factor analysis of adult and childhood stress variables was conducted to observe how much variance was shared by the various SES/stress predictor variables. A principal components factor analysis with a promax rotation was used. A promax rotation is an oblique rotation that allows variables to be interrelated with each other. As shown in Figure 2, only one factor had an eigenvalue greater than 1. Using the Kaiser and Guttman rule, which suggests preserving those factors with an eigenvalue of 1 or greater, one sole factor was retained (Guttman, 1953).

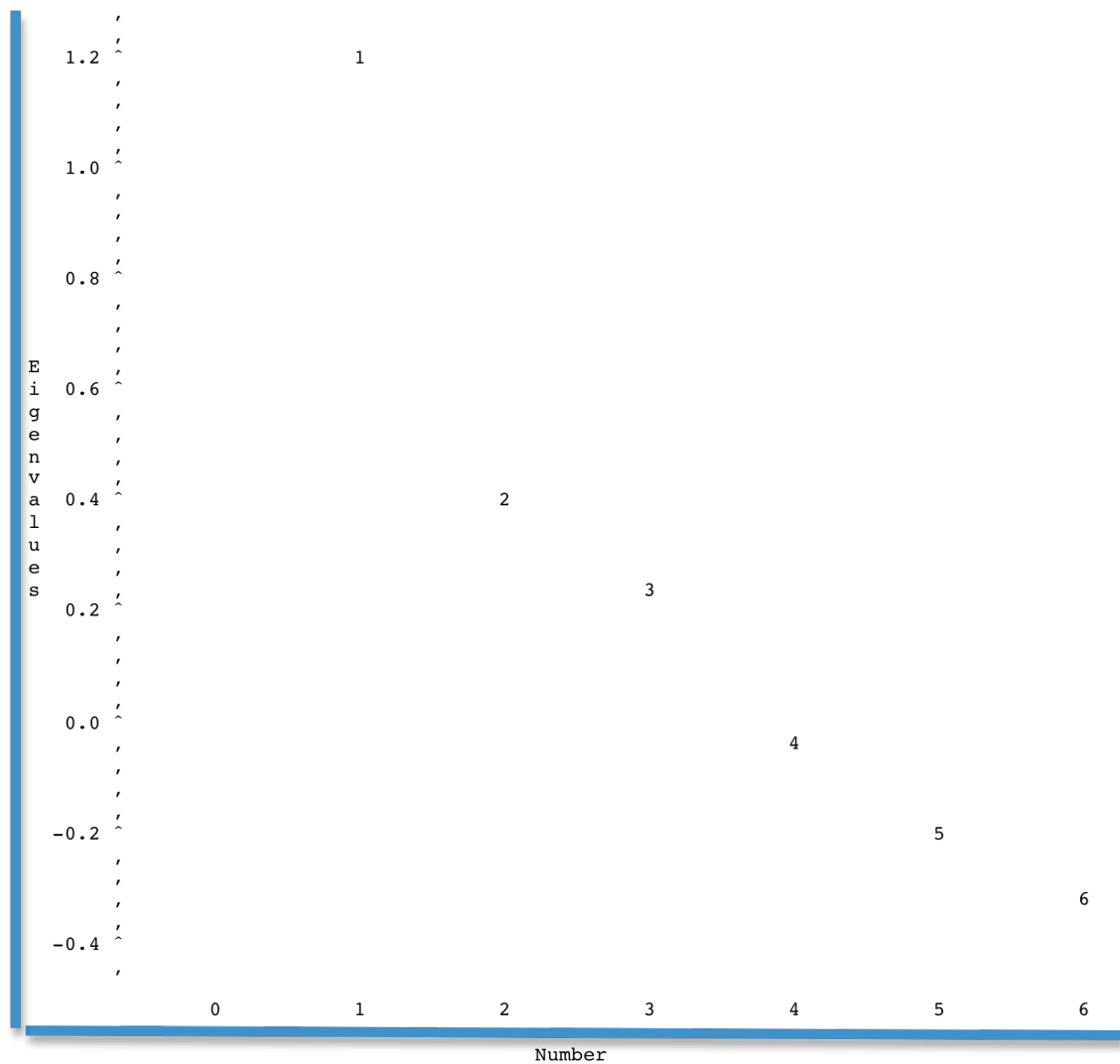


Figure 2: Scree Plot of Eigenvalues

As shown in Table 5, the one factor solution is driven by a strong effect of mother and father's education on this factor. From this exploratory factor analysis, it was concluded that mother's and father's education are similarly strong drivers of a

SES/stress effect that was intended to be tested as a predictor of total 24 hour calorie intake, trunk and total fat.

Table 5: Results of Exploratory Factor Analysis

Variable	Factor 1	Factor 2	Factor 3
Household count	0.12085	0.46519	-0.15803
Income	0.10773	0.40799	0.22586
Self Education	0.25219	-0.14024	0.33283
Father Education	0.75059	-0.01956	-0.08233
Mother Education	0.74369	-0.07170	-0.04689
PSS	-0.03222	-0.09923	-0.23252
Variance Explained By Each Factor			
	Factor 1	Factor 2	Factor 3
	1.2073125	0.4178943	0.2498030

To explore how each of these SES/stress variables related to a common single factor, a confirmatory factor analysis was conducted on variables loading on a single forced factor. If deemed strong predictors, those whose SES factor loadings rank highest on this construct may be used as the environmental variable in GxE interaction models to predict outcome measures.

A number of SES-related and stress-related factors were loaded onto one factor that labeled “SES/Stress.” These variables included: current household income, individuals in the household, individual education, father’s education, mother’s education, and the Perceived Stress Scale (PSS). As shown in Table 6, mother and father’s education had the greatest loadings, both when PSS was included in the factor

($t=12.69, 12.45$, respectively) and also when PSS was removed from the factor ($t=12.66, 12.42$). Both father's and mother's education were equally strong predictors of this SES/Stress factor. The next strongest predictor, self-education, was less than half as strongly associated with this factor (with PSS: $t= 5.15$, without PSS: $t= 5.14$).

Table 6: Factor Loading of SES Stress and Other Stress Predictors on a Single Factor

Standardized Factor Loading Matrix:	
	Estimate/ Std Err/ t-value
	SES Stress
HOUSEHOLD COUNT	0.1175
	0.0443
	2.6513
INCOME	0.0526
	0.0447
	1.1756
SELF EDUCATION	0.2220
	0.0431
	5.1473
FATHER EDUCATION	0.8538
	0.0673
	12.6890
MOTHER EDUCATION	0.7825
	0.0628
	12.4535
PSS	-0.0132
	0.0448
	-0.2955

Mother and father's education appear to be the best predictors of SES/stress among available variables. The first exploratory factor analysis suggests that one factor emerges as the best predictor of these variables. When forced to load on one SES/Stress factor, mother and father's education emerge as unique predictors of this single factor.

Given these results, both parents' education variables were included as environmental predictors in GxE interactive models.

Because of their putative contribution to caloric intake and fat composition in this study and extensive use in previous studies (Bentley & Widom, 2009; Block, He, Zaslavsky, Ding, & Ayanian, 2009; Howe, et al., 2010), analyses seeking to uncover GxE contributors of caloric intake and fat composition controlled for age, sex, race, work and leisure activity. Demographic covariates include age, sex, and race. Health behavior covariates include work and leisure activity. Both types of activity were included because this study was seeking to identify non-physical activity contributors to eating and fat composition. Obligatory model covariates include height, which is required to adjust trunk and total fat measurements, and income, which is required to adjust for current SES status. Current smoking habits were not included in models due to 541 missing data points.

7.3.4 Mediation Analysis

As shown in **Figure 3**, mediation was to be tested according to procedures outlined in (Hayes, 2009). First it was planned to 1) determine whether a parents' education by DRD2 SNP interaction significantly predicts (c') obesity, then 2) determine whether the parents' education by DRD2 SNP interaction significantly affects (a) total calorie consumption, 3) determine that total calories has a significant main effect (b) on obesity, and finally 4) determine that the effect of the stress by DRD2 SNP interaction on obesity

(c') shrinks upon the addition of total calorie consumption (M) to the model.

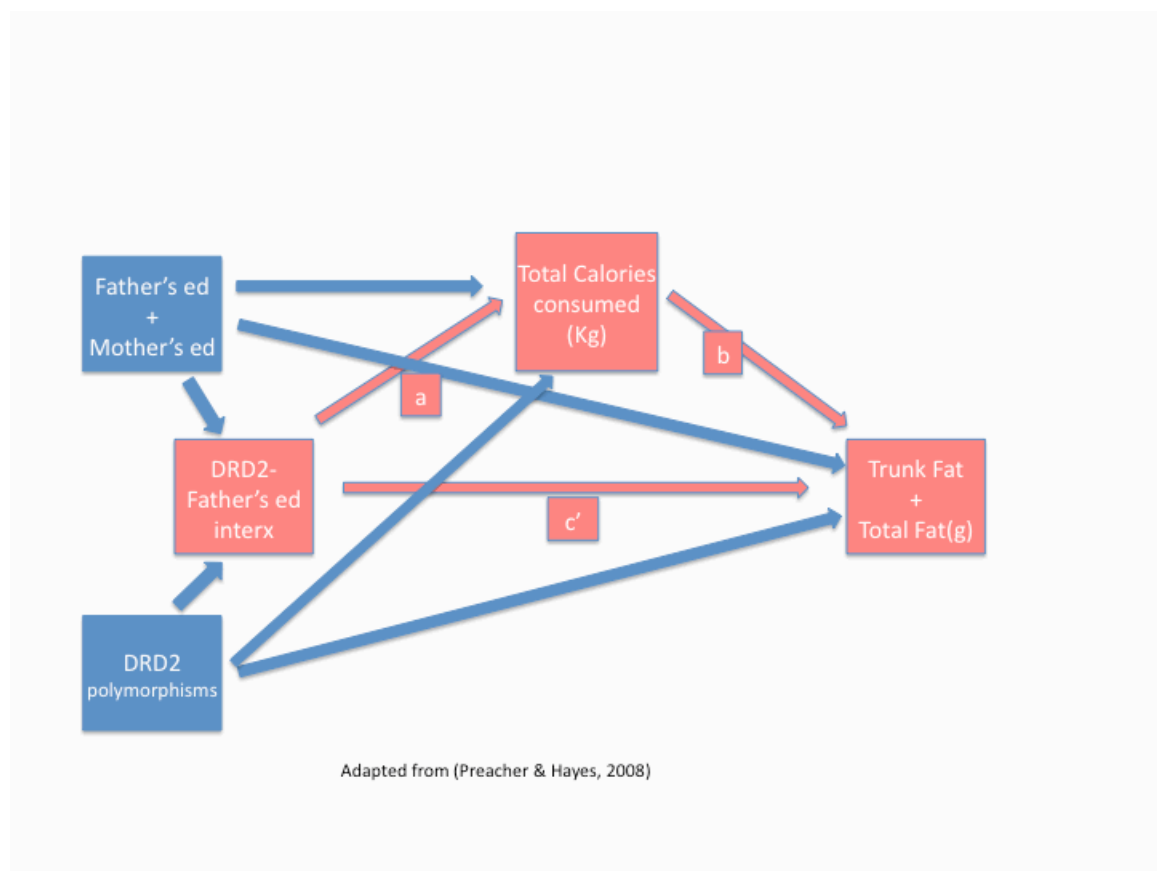


Figure 3: Mediation Model

Each model with the parents' education by DRD2 SNP interaction also includes lower order main effects of parents' education alone and the DRD2 SNP alone. These main effects will predict either trunk fat, total fat, or total calorie consumption, depending on the particular task at hand. Main effects will be reported only in cases where the higher-order interaction is not a better descriptor of the data.

7.4 Statistical Analysis

7.4.1 Distribution of Variables

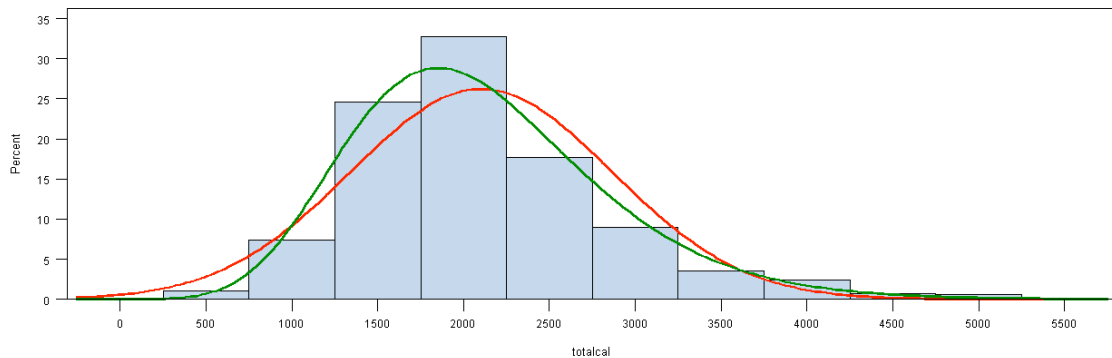


Figure 4: Histogram of '24-Hour Total Calories' Variable with Normal (Red) and Log-Normal (Green) Distribution Lines

As shown in Figure 4, the distribution of the total calories variable, an index of calories consumed in a 24-hour diet recall, is skewed (1.08), kurtotic (2.03) and non-normal. Moreover, the histogram in Figure 4 shows that a log-normal line (green) is a better curve for the data than a normal (red) line. When a simple non-linear log transformation was performed to adjust the variable normality, an outlier was discovered who reported consuming 32.81 calories. This outlier was, by itself, causing a deviation of the distribution from normality and conflicting with a Gaussian analysis of the data, and therefore it was removed from future analyses.

To choose a standard and replicable transformation, a log transformation was chosen. This step reduced the skew to -0.28 and the kurtosis to 1.39. Figure 5 shows a histogram of the transformed total calorie variable and the same two distributions. They are overlapping in this histogram, suggesting that the normal distribution is the most parsimonious distribution for the transformed variable.

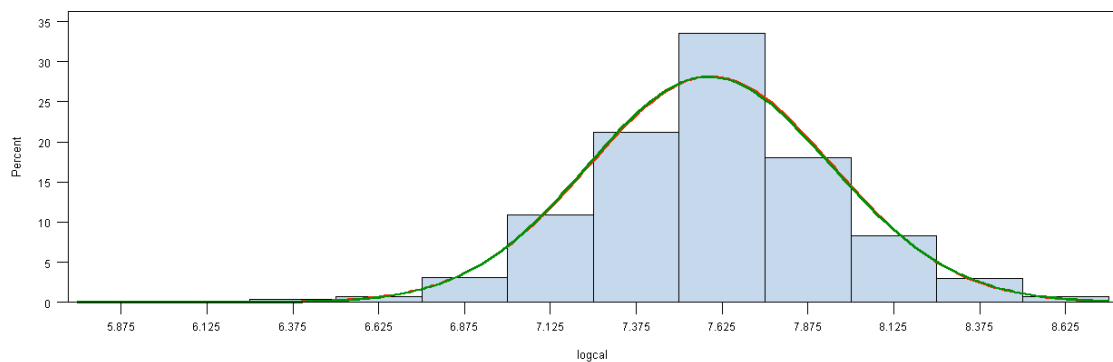


Figure 5: Histogram of Log-Transformation of '24-Hour Total Calories' Variable with Normal (Red) and Log-Normal (Green) Distribution Lines

Other outcome variables including trunk fat and total fat measured by DXA scan approximated a normal distribution with skewness and kurtosis values below 1, therefore standard Gaussian methods were employed. Proc Mixed was used to model all mixed models on SAS software, Version 9.2 of the SAS system for Windows, copyright © 2008.

In Proc Mixed, a random intercept was estimated to control for the effect of family membership on outcome variables. A random slope was estimated for mother and father's education by family; however, this did not add significantly to the

predictive power of the model or reduce the primary fit statistics (e.g., AIC, BIC, -2 residual log likelihood). An added slope reduced model parsimony and caused the model to become overspecified. Therefore, only a random family intercept was used in final models.

As modeled in **Figure 1**, it was hypothesized that childhood socioeconomic stress as a main effect may or may not have a direct effect on either eating behavior or obesity. As the literature reviews suggest, this literature is mixed, particularly depending on the type of SES measure used. It was predicted that childhood SES (i.e., mother's and father's education) would demonstrate a trend toward predicting both outcome variables without being significant predictors. Likewise, the literature on the main effect of DRD2 polymorphisms on eating behavior and obesity is mixed. A small trend toward predicting both outcome variables was predicted.

It was also predicted that the interaction between stress and DRD2 SNPs would significantly predict both total calories and obesity. Since greater evidence regarding effects on behavior exists for SNPs RS1800497, RS1076560 and to a lesser extent for RS1116313, it was predicted that GxE interactions using these polymorphisms would be better predictors of both eating behavior and obesity than RS1124492, about which nothing has been published but did emerge from the SNP analysis covering the DRD2 gene. The mediator, total calories, was hypothesized to significantly predict obesity. The effect of the interaction between parental education and DRD2 SNPs predicting obesity was expected to shrink upon the addition of eating behavior to the model (Preacher & Leonardelli, 2001).

In sum, it was expected that the findings would support the premise that those with high stress and a vulnerable dopaminergic reward system (i.e., operationalized as weak DRD2 transmission and indexed by DRD2 SNPs) would engage in greater eating behavior (i.e., consume more total calories). Moreover, eating behavior was expected to predict a greater part of the variance predicting obesity status (i.e., operationalized as trunk fat and total body fat).

7.4.2 Significance Testing

In order to describe GxE interactions with a meaningful measure of parental education to use as a categorical variable, the variable was reduced from 21 categories to three variables representing tertiles of educational attainment. This breakdown of educational categories was necessary to provide adequate cell sizes to elucidate complex interactive relationships present in the data.

Table 7 shows the breakdown of years of education into three subgroups. Significance testing was determined by the F-test and associated p-value for the Type 3 sum of squares. If a significant parental education by genotype interaction was revealed, then this interaction was probed by conducting follow-up comparisons using the LSMESTIMATE statement in the SAS software v9.2.

Table 7: Parental Education Tertiles

Number Label	Mother's/Father's Education Level	Number of Participants
1	0 - 12th grade	187
2	13th - Undergraduate College Diploma	317
3	Graduate School and Greater	147

8. Results

8.1 Descriptive Statistics

As shown in Table 8, the sample is a fairly diverse with a mean age of 31 and a standard deviation of 12 years. The sample was 35% African American, 65% Caucasian. In terms of covariates that might influence calorie consumption or weight, individuals were found on the moderate to average physical activity level. The most common self-described level of physical activity while on the job was “moderately active” (38%) followed by “active” (26%). The most common self-described level of physical activity outside of work was “moderately active” (49%) followed by “active” (33%).

Table 8: Descriptive Statistics

Variable	Mean (\pmstd)		
Sex	60.9% F / 39.1% M (424 / 272)		
Race	35.2% B / 64.8% W (245 / 451)		
Age (SD)	30.63 (\pm 11.45)		
Work Activity	Category	N	%
	Sedentary	139	20.72
	Mod. Active	253	37.70
	Active	176	26.23
	Heavy Work	25	3.73
	Not Working	78	11.62
Leisure Activity	Category	N	%
	Sedentary	55	8.20
	Mod. Active	327	48.73
	Active	224	33.38
	Comp. Sports	65	9.69
Income	\$60,000-\$64,999 (\pm \$35,000)		
Mother's Education (years)	14.96 (\pm 3.17)		
Father's Education (years)	15.11 (\pm 3.89)		
RS1076560genotype	Alleles	N	%
	A / A	13	2.55
	A / C	130	25.49
	C / C	367	71.96

RS1116313genotype	Alleles	N	%
	C/C	118	23.05
	C/T	237	46.29
	T/T	157	30.66
RS1124492genotype	Alleles	N	%
	A/A	35	5.66
	A/C	170	27.51
	C/C	413	66.83
RS1800497genotype	Alleles	N	%
	A/A	41	10.73
	A/G	146	38.22
	G/G	195	51.05

In terms of socioeconomic status, the mean total household income (i.e., including all wages, income, social benefits, retirement funds, social security, etc. for the past year) was \$60,000-\$64,999, but with a standard deviation of about \$35,000, indicating significant variation. Mean father's education was 15 years (i.e., an associate's degree) with a standard deviation of 4 years of school. Mean mother's education was also 15 years (i.e., an associate's degree), with a standard deviation of 4 years of school.

Table 9: Missing Genotype Data

Genotype	Missing #
RS1076560	218
RS1116313	216
RS1124492	80
RS1800497	346

As shown in Table 9, each of the genotypes was missing data, some more than others. The prRS1076560 genotype was missing 218 individuals, the prRS1116313 genotype was missing 216, the prRS1124492 genotype was missing 80 and the RS1800497 genotype was missing 346.

Among the alleles of the four genes, some were more evenly distributed than others. With all of the participant data aggregated together, three of the four SNPs

frequencies were in accordance with Hardy-Weinberg (HW) equilibrium, and the p values were >0.05 (Rodriguez, Gaunt, & Day, 2009). The RS1124492 genotype was not in Hardy-Weinberg equilibrium ($p<0.005$, $\chi^2=9.05$), however as shown in Table 10, all genes are within HW equilibrium when stratified by race.

Therefore in accordance with previous research (Uddin, et al., 2010), all models were adjusted for race and report results were adjusted for race unless otherwise specified. Despite the finding of one SNP violating HW equilibrium in the larger sample, since allelic variance in racial subgroups was within HW equilibrium and analyses adjusted for these racial subgroups, analyses reflect a sample within HW equilibrium (Rodriguez, et al., 2009). Moreover, adjusting for self-reported racial categorization in this manner has been shown to correspond well with ancestral classification using genetic markers (Tang, et al., 2005).

Table 10: Hardy-Weinberg Equilibrium Chi-Sq Tests Stratified By Race

Genotype	Race	χ^2	p-value
RS1076560	Bl	1.5 1	0.2187
RS1116313	Bl	0.99	0.3216
RS1124492	Bl	1.43	0.2319
RS1800497	Bl	1.10	0.2947
RS1076560	Wh	0.16	0.6883
RS1116313	Wh	1.03	0.3097
RS1124492	Wh	0.34	0.5621
RS1800497	Wh	0.04	0.8333

Table 11: Missing Data By Variable

Variables	Missing #
Age, Sex, Race	2
Work & Leisure Activity	27
Height	116
Income	42
Mother's Education	46
Father's Education	56
24-H Calorie Recall	154
Trunk & Total Fat	126

As shown in Table 11, several variables had missing data. Note that many of those individuals with missing data on one variable were missing on multiple variables, so much of this missingness overlaps. For example, all individuals missing trunk fat were also missing total fat measurements. Many anthropometric measurements were also taken concurrently, so for example only 4 individuals who provided trunk and total fat measurements did not provide height. Note that current smoking status was not included as a covariate since 541 out of 647 individuals were found to be missing smoking data.

As shown in Table 12, age, sex, leisure activity were significant predictors of total calorie intake in models consisting of non-obligatory covariates predicting outcome variables. Specifically, young and male participants consumed more calories. Those sedentary and in competitive sports consumed more than those active or moderately active. Work activity trended toward predicting total calorie intake, such that those active at work tended to consume more than other groups ($F(4,525)=2.19$, $p=0.0686$).

Table 12: Model of Covariates Predicting Log of 24-Hour Total Calorie Intake

Variable	Num DF	Den DF	F	p-value
Age	1	525	5.92	0.015
Sex	1	525	133.95	<.0001
Race	1	525	0.92	0.337
Work Activity	4	525	2.19	0.069
Leisure Activity	3	525	2.87	0.036

Tables 13 and 14 show that age, sex, race and leisure activity were significant predictors of trunk fat and total body fat (i.e., total fat). Specifically, older, Black, and female participants had more trunk and total body fat. Those sedentary and moderately active had more trunk and total fat than other groups.

Table 13: Model of Covariates Predicting Trunk Fat

Variable	Num DF	Den DF	F	p-value
Age	1	556	97.99	<.0001
Sex	1	556	119.53	<.0001
Race	1	556	8.04	0.005
Work Activity	4	556	0.86	0.489
Leisure Activity	3	556	22.19	<.0001

Table 14: Model of Covariates Predicting Total Body Fat

Variable	Num DF	Den DF	F	p-value
Age	1	556	80.90	<.0001
Sex	1	556	341.42	<.0001
Race	1	556	5.03	0.025
Work Activity	4	556	0.80	0.527
Leisure Activity	3	556	22.38	<.0001

8.2 Multicollinearity

Multicollinearity, the problematic statistical phenomenon in which two or more predictor variables in a multiple regression model are highly correlated, was tested using measurements of tolerance and variance inflation produced by the Proc Reg procedure in the SAS software v9.2. The standard cutoff of less than 1 for tolerance estimates and greater than 10 for variance inflation estimates were used to indicate multicollinearity (Menard, 1995). Results for all tolerance parameters for all covariates, father's and mother's education predicting the three outcomes variables of interest were less than the 1, and therefore all variance inflation estimates, which are calculated as the inverse of tolerance estimates, were also less than 10. These tests suggest an absence of multicollinearity and the statistical appropriateness of using each of the prescribed covariates.

8.3 Interaction Effect Analyses

Separate analyses were conducted for a father's education x genotype interaction and a mother's education x genotype interaction predicting 24-hour total calorie intake, trunk fat (% of body weight) and total fat (% of body weight). Father's education by genotype interactions were not significant predictors of any outcomes. Father's education was also not a significant main effect predictor of any outcomes in Type 3 Sum of Squares models, and therefore will not be repeated further. Significant mother's education by genotype interactions are described below.

8.3.1 Mother's Education x Genotype Predicts Calorie Consumption

Separate analyses were conducted for each DRD2 SNP and mother's education (viz. by tertiles as shown in Table 7) main effects and a mother's education by genotype interaction predicting 24-hour total calorie intake. Table 15 shows that no main effects or interactions with mother's education were significant predictors of calorie consumption. All interactions controlling for the additional height covariate were also non-significant ($p>0.05$).

Table 15: Mother's Education by Genotype Interactions Fail to Predict Total Calorie Consumption

Effect	NumDF	DenDF	FValue	ProbF
1ST SNP				
MOTHER'S EDUCATION	2	188	0.32	0.7296
RS1076560	2	188	1.56	0.2119
MOTHER'S ED * RS1076560	3	188	0.09	0.9655
2ND SNP				
MOTHER'S EDUCATION	2	188	0.8	0.4516
RS1116313	2	188	0.83	0.4374
MOTHER'S ED * RS1116313	4	188	0.82	0.5152
3RD SNP				
MOTHER'S EDUCATION	2	214	0.32	0.7277
RS1124492	2	214	0.13	0.8825
MOTHER'S ED * RS1124492	4	214	0.12	0.9736
4TH SNP				
MOTHER'S EDUCATION	2	130	1.22	0.2989
RS1800497	2	130	2.01	0.1387
MOTHER'S ED* RS1800497	4	130	1.36	0.25

Note: This and following tables are controlled for standard covariates not pictured

Table 16 shows the correlations between trunk, total body fat, and total calories and percent of diet that is carbohydrates, protein, dietary fat, and dietary saturated fat as dietary components. A strong negative correlation existed between the log of total calories in a 24-hour diet recall and trunk fat (coef.= 0.26) and between total calories and total body fat (coef.=0.34). However, no correlations existed between the trunk and total fat outcomes and the components of the diet.

Table 16: Correlations Between Trunk Fat, Total Fat and Total Calories, Dietary Components

Pearson Correlation Coefficients Number of Observations					
	Lg-Total Calories	Carb %	Protein %	Fat %	SatFat %
Total Fat	-0.33941 531	-0.04585 530	-0.02964 531	0.03844 531	0.05896 520
Trunk	-0.26174 531	-0.06562 530	-0.04045 531	0.05568 531	0.07654 520

As shown in Table 17, follow-up analyses of the relationship reveal that, despite a strong negative correlation between total calories and trunk and total body fat, the log of total calories was not associated with trunk fat ($b=0.76$, $p=0.43$) or total body fat ($b=0.46$, $p=0.572$), after controlling for standard covariates (i.e., sex, age, race, height, work activity, leisure activity). Models run with the non-transformed total calories variable predicting trunk ($b=0.00006$, $p=0.895$) and total fat ($b=-0.00005$, $p=0.896$) area also non-significant.

Table 17: Transformed and Non-transformed Total Calorie Variable Fails to Predict Body Fat

Effect	NumDF	DenDF	FValue	ProbF
Log of Total Calories				
Trunk Fat	1	236	0.55	0.4296
Total Fat	1	236	0.32	0.5721
Total Calories				
Trunk Fat	1	236	0.02	0.8952
Total Fat	1	236	0.02	0.8962

8.3.2 Mother's Education x Genotype Interaction Predicts Trunk Fat

Table 18 shows the results of separate analyses conducted for a mother's education by genotype interaction predicting trunk fat. One higher order mother's education by the RS1116313 genotype interaction significantly predicted trunk fat. Figure 6 shows the interaction between tertiles of mother's education and the RS1116313 genotype that predicts trunk fat ($F(4,191)=2.94$, $p=0.022$). Apart from RS1116313, a significant and a trend main effect of mother's education are also shown in Table 18 for RS1124492 ($F(2,237)=4.25$, $p=0.015$) and RS180097 ($F(2,191)=2.44$, $p=0.091$) SNPs.

Table 18: Mother's Education by Genotype Interactions Predict Trunk Fat

Effect	NumDF	DenDF	FValue	ProbF
1ST SNP				
MOTHER'S EDUCATION	2	191	1.44	0.239
RS1076560	2	191	1.19	0.3054
MOTHER'S ED * RS1076560	3	191	0.92	0.4327
2ND SNP				
MOTHER'S EDUCATION	2	191	3.68	0.0269

RS1116313	2	191	3.79	0.0242
MOTHER'S ED * RS1116313	4	191	2.94	0.0216
3RD SNP				
MOTHER'S EDUCATION	2	237	4.25	0.0153
RS1124492	2	237	0.74	0.4763
MOTHER'S ED * RS1124492	4	237	0.99	0.4124
4TH SNP				
MOTHER'S EDUCATION	2	133	2.44	0.0913
RS180097	2	133	0.25	0.7753
MOTHER'S ED*RS180097	4	133	0.77	0.5487

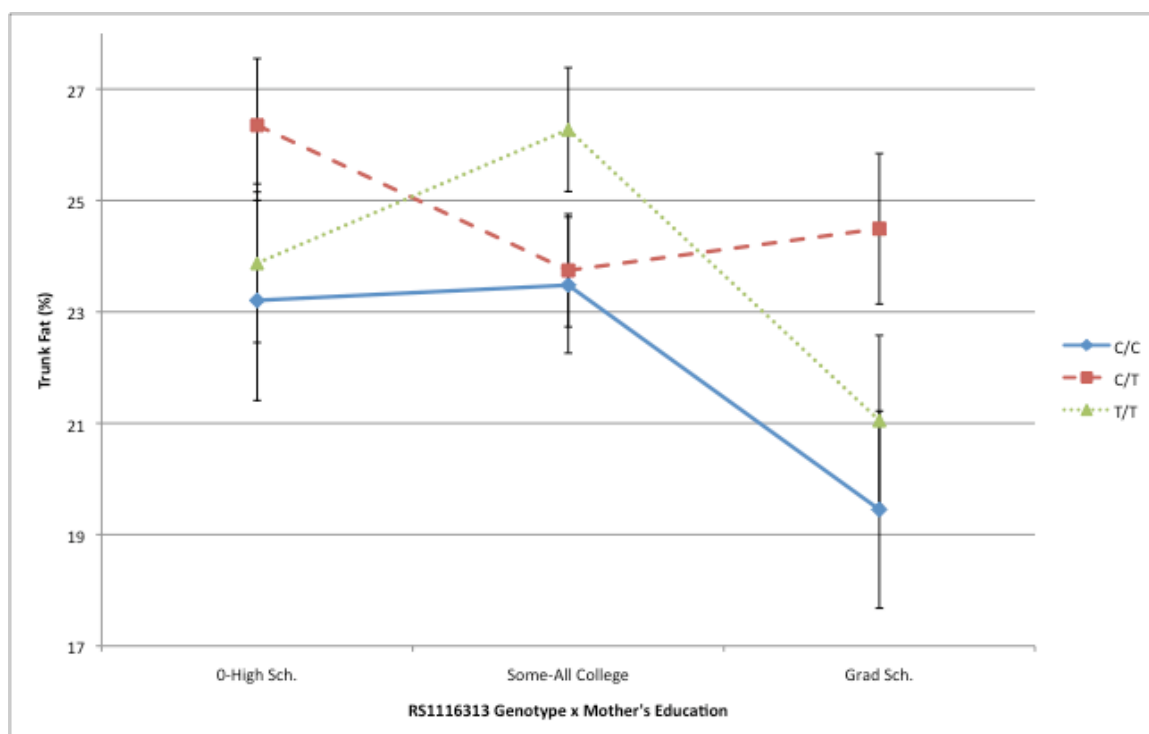


Figure 6: Mother's Education by RS1116313 Interaction Predicts Trunk Fat

As shown in Figure 6, the interaction between tertiles of mother's education and RS1116313 predicting trunk fat is driven by a pattern whereby, as a mother's education

increases, trunk fat decreases in the highest tertile for C/C and T/T genotypes. In contrast, trunk fat does not decrease for C/T heterozygotes as one's mother's education increases. Post-hoc comparisons revealed that the mean Trunk Fat of those with C/C or T/T genotypes in the highest mother's education tertile were both significantly lower than the combined mean of low and medium mother's education groups ($b=3.96$, $p=0.004$). In contrast the C/T's with high mother's education were not different from the combined low/med mother's education groups with C/T ($b=0.55$, $p=0.696$).

Within the high mother's education group, those with C/T genotype had significantly higher trunk fat than either C/C or T/T ($b=-4.24$, $p=0.007$). This effect follows a molecular heterosis pattern whereby homozygotes are similar but differ from the heterozygotes on a participar phenotype (Comings & MacMurray, 2000).

8.3.3 Mother's Education x Genotype Predicts Total Fat

One RS1116313 by mother's education interaction significantly predicted total fat. Table 19 and Figure 7 show the interaction between mother's education and the RS1116313 genotype that predicts total body fat ($F(4, 191)=3.94$, $p=0.004$). Apart from RS1116313, a significant main effect of mother's education is also shown in Table 19 for the RS1124492 ($F(2,237)=4.91$, $p=0.008$) SNP.

Table 19: Mother's Education by Genotype Interactions Predict Total Body Fat

Effect	NumDF	DenDF	FValue	ProbF
1ST SNP				
MOTHER'S EDUCATION	2	191	0.96	0.3834
RS1076560	2	191	0.84	0.4343

MOTHER'S ED * RS1076560	3	191	0.59	0.6234
2ND SNP				
MOTHER'S EDUCATION	2	191	3.99	0.0201
RS1116313	2	191	4.69	0.0103
MOTHER'S ED * RS1116313	4	191	3.94	0.0043
3RD SNP				
MOTHER'S EDUCATION	2	237	4.91	0.0081
RS1124492	2	237	1.04	0.3566
MOTHER'S ED * RS1124492	4	237	0.79	0.5354
4TH SNP				
MOTHER'S EDUCATION	2	133	2.26	0.1087
RS1800497	2	133	0.44	0.6449
MOTHER'S ED*RS1800497	4	133	0.96	0.4296

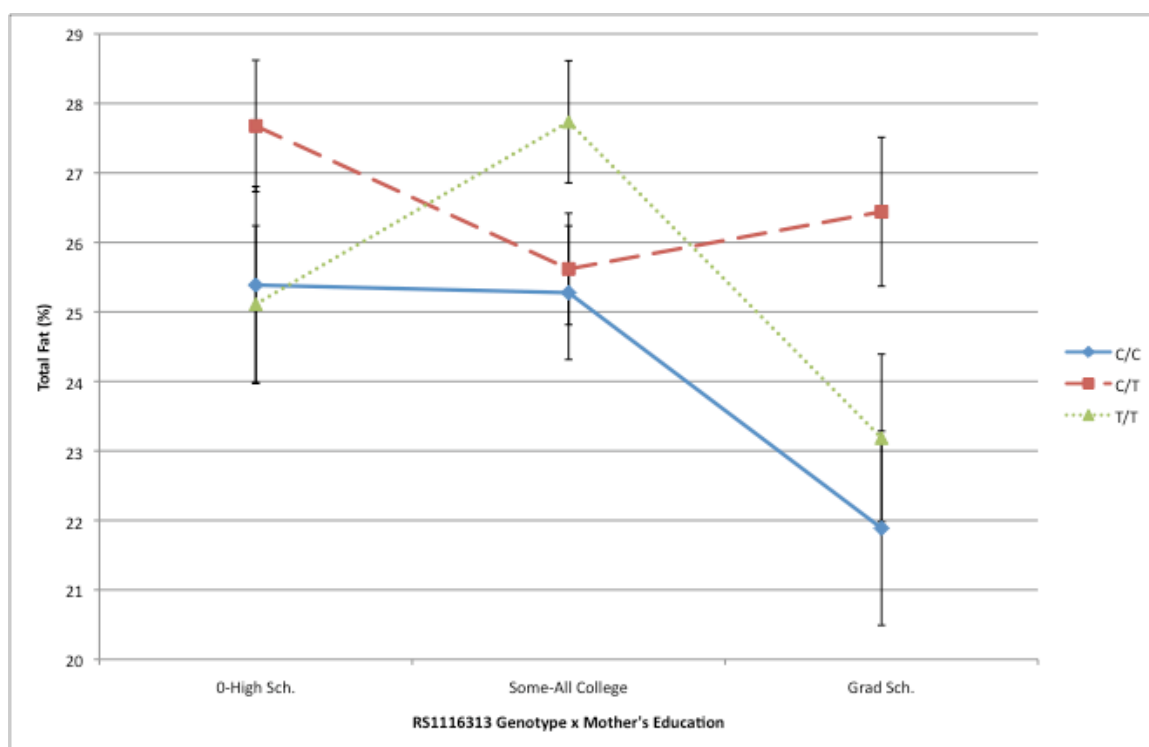


Figure 7: Mother's Education by RS1116313 Genotype Interaction Predicts Total Fat

As shown in Figure 7, the interaction follows a similar pattern as the previous model predicting trunk fat. The interaction between mother's education and RS1116313 predicting total body fat is driven by a pattern whereby, as a mother's education increases, total fat decreases in the highest mother's education tertile for C/C and T/T genotypes. In contrast, total fat does not decrease for C/T heterozygotes as one's mother's education increases. Instead for C/T heterozygotes, total fat stays fairly constant across educational categories.

Post-hoc comparisons revealed that the mean Total Fat of those with C/C or T/T genotypes were both significantly lower in the highest mother's education tertile than C/C's or T/T's averaged over the combined low and medium mother's education groups ($b=3.34$, $p=0.002$). In contrast the C/T's with high mother's education were not different from the combined low/med mother's education groups with C/T ($b=0.21$, $p=0.855$). Within the high mother's education group, those with C/T genotype had significantly higher total fat than either C/C or T/T ($b=-3.90$, $p=0.002$), again presenting a molecular heterosis pattern (Comings & MacMurray, 2000).

8.4 Mediation Analysis

Since no parental education by genotype interaction significantly predicted total calories in a 24-hour diet recall, no mediational analyses of the original hypothesis were possible. Baron and Kenny (1986) propose that three criteria must be met to test the effect of mediation. First, one must show that the initial variable (i.e., the GxE interaction in this case) is correlated with the outcome. Then, one must show that the initial variable

is correlated with the mediator. Next, one must show that the mediator, controlled for the initial variable, affects the outcome variable. Finally, to establish that the mediator completely mediates the relationship between the initial variable and the outcome, the effect of X on Y controlling for M should be zero. In practice, this final step is rarely satisfied.

Since the interaction of mother's education and the RS1116313 genotype only predicted the outcomes of trunk fat and total fat, but did not predict any of several possible dietary mediators, meditational analyses were not possible.

8.5 Post-Hoc Analyses

8.5.1 Predicting Leisure Activity For the RS116313 Genotype

Knowing that exercise has been linked with dopaminergic receptor expression (Roberts, et al., 2012), the same mother's education by RS1116313 interaction was treated as a predictor of leisure exercise as a possible mediator of the relationship with body fat composition. As shown in Table 20, the interaction was not a significant predictor of leisure time exercise as a continuous variable. Attempts to predict leisure time exercise as an ordinal categorical variable did not converge.

Table 20: Interaction Between Mother's Education and RS1116313 Fails to Predict Leisure Physical Activity

Variable	NumDF	DenDF	F value	Pr >F
Mother's Ed	2	246	2.20	0.1133
RS1116313	2	246	1.34	0.2639
Mother's Ed * RS1116313	4	246	0.45	0.7699

8.5.2 Predicting Dietary Components For All Genotypes

Knowing that total calories from a 24-hour diet recall was not explained by mother's education by DRD2 genotype interactions, components of the participants' diets were analyzed. By analyzing percentage of calories made up of carbohydrates, protein, fat, and saturated fat, an exploratory analysis of dietary components was undertaken to perhaps better explain the significant outcome models.

The same covariates in models predicting total calories from a 24-hour diet recall were used to predict dietary components. When mother's education by genotype interactions were tested for the separate components of dietary intake, there were significant mother's education by RS1800497 interactions for dietary fat ($F(4,130)=2.44$, $P=0.05$) and protein ($F(4,130)=3.26$, $P=0.01$) and mother's education by RS1124492 for dietary fat ($F(4,214)=2.44$, $P=0.048$). Tables 21-23 and Figures 8-10 display these significant models.

Table 21: Mother's Education By RS1800497 Interaction Predicts Percent of Calories from Dietary Fat

Dietary Fat				
Effect	NumDF	DenDF	FValue	ProbF
MOTHER ED	2	130	3.85	0.0237

RS1800497	2	130	5.08	0.0075
M ED* RS1800497	4	130	2.44	0.0504

Table 22: Mother's Education by RS1800497 Predicts Percent of Calories from Protein

Protein				
Effect	NumDF	DenDF	FValue	ProbF
MOTHER ED	2	130	2.49	0.0872
RS1800497 genotype	2	130	0.95	0.388
M ED*RS1800497	4	130	3.26	0.0139

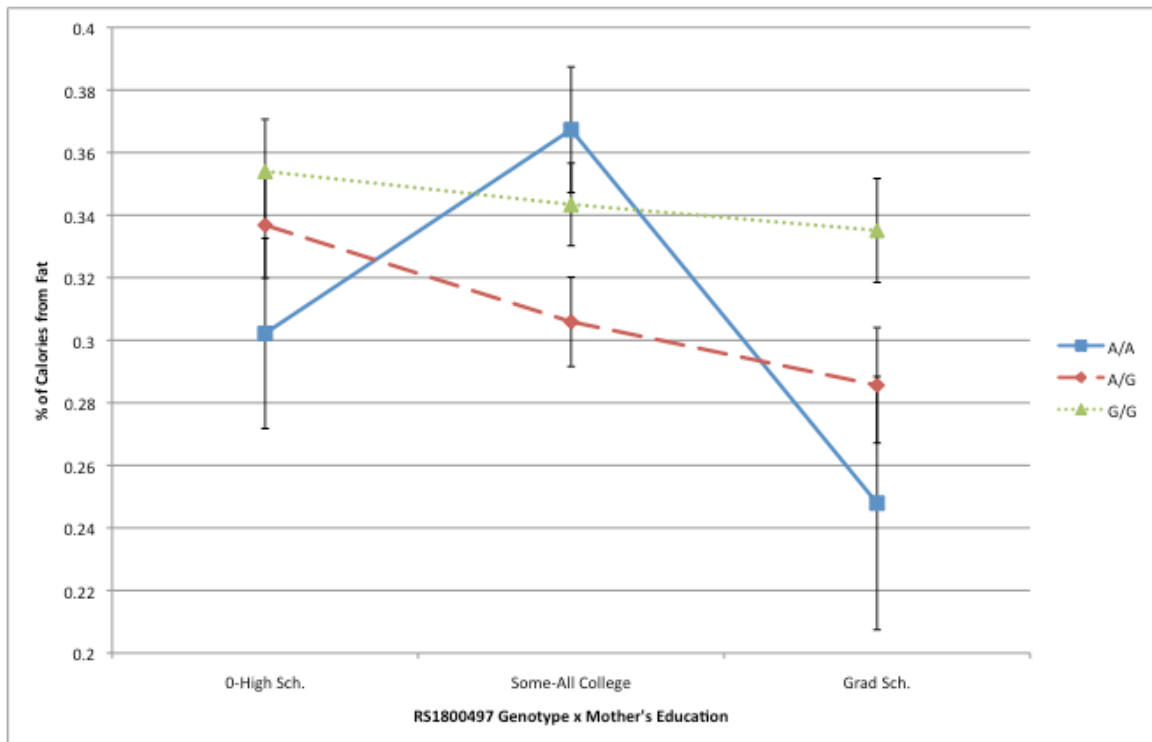


Figure 8: Mother's Education by RS1800497 Interaction Predicts Percent of Calories from Dietary Fat

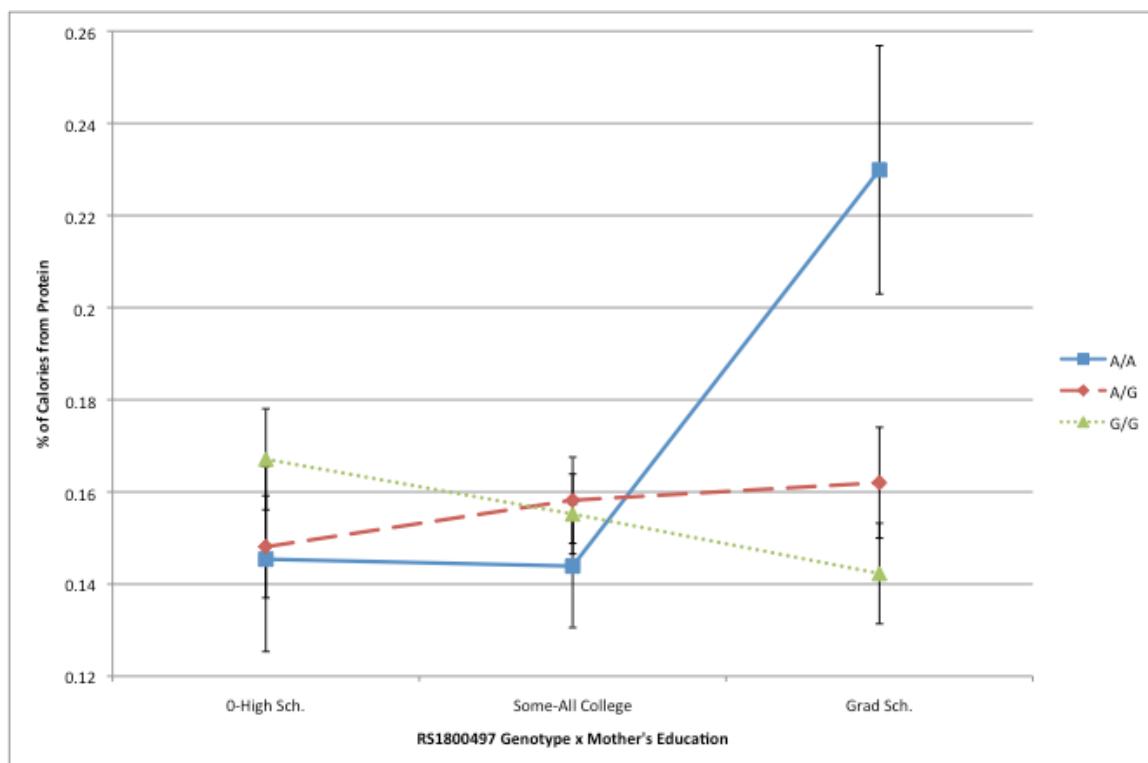


Figure 9: Mother's Education by RS1800497 Interaction Predicts Percent of Calories from Protein

Figures 8 and 9 show that the interactions were primarily driven by differences between A/A homozygotes and those with other genotypes in the high mother's education tertile. A-allele carriers in the highest mother's education tertile consumed a lower percent of calories from fat ($b=0.037$, $p=0.006$) and a greater percent of calories from protein ($b=0.08$, $p=0.007$) compared with other RS1800497 allele by mother's education combinations.

Table 23: Mother's Education by RS1124492 Interaction Predicts Percent of Calories from Dietary Fat

Dietary Fat				
Effect	NumDF	DenDF	FValue	ProbF
MOTHER ED	2	214	2.73	0.0677
RS1124492	2	214	0.52	0.5974
M ED*RS1124492	4	214	2.44	0.0481

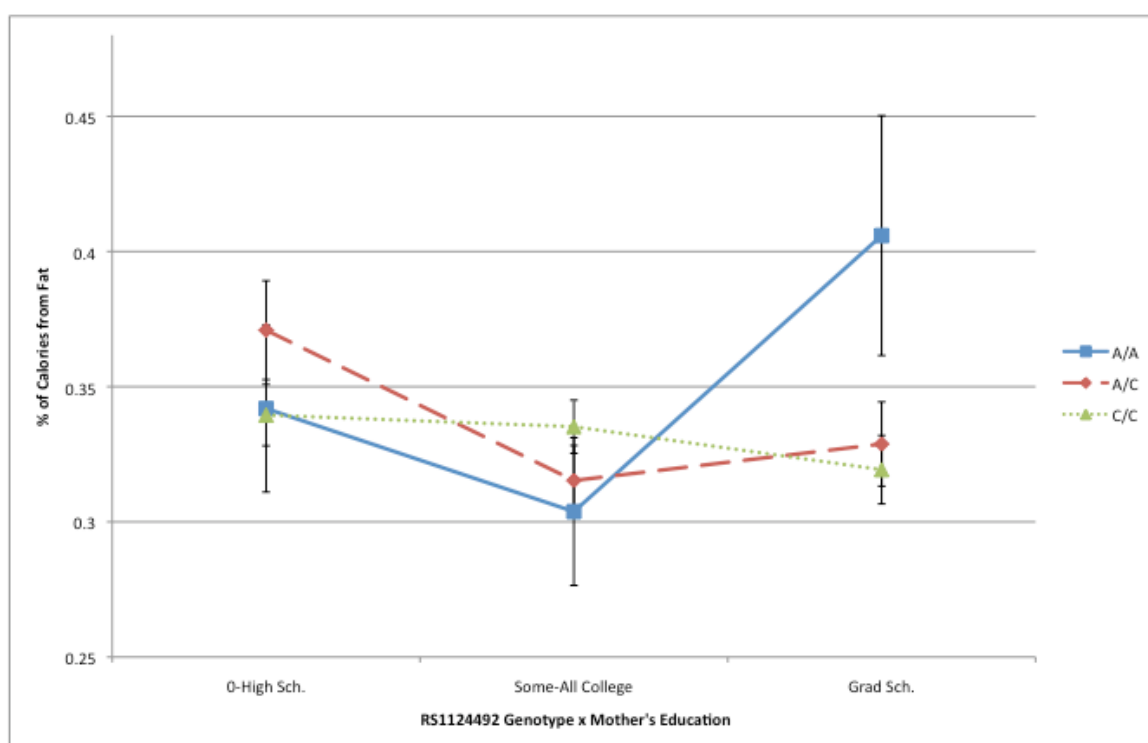


Figure 10: Mother's Education by RS1124492 Interaction Predicts Calories from Dietary Fat

In Figure 10, A / A RS1124492 homozygotes displayed a different pattern than other genotypes. Namely, there was a trend for A / A carriers with a high mother's

education to consume a greater percent of calories from fat than other groups ($b=0.08$, $p=0.069$). Whereas A/C and C/C carriers seemed to reduce percent of calories from fat with greater mother's education, A/A homozygotes increased.

8.5.4 SNP Proxy Search For RS1116313 SNP

Since few articles have been published on RS1116313, SNAP Proxy Search Version 2.2 by the Broad Institute was used to identify other SNPs in high linkage disequilibrium (LD) with RS1116313. The instrument is limited to identifying SNPs within 500 base pairs of RS1116313. Table 24 lists all 27 SNPs in high LD with RS1116313 provided by the program. These SNPs are discussed in the Discussion section below.

Table 24: SNPs in High Linkage Disequilibrium with RS1116313

Proxy	Distance	RSquared	DPrime
rs1076563	198	1	1
rs12808482	1109	1	1
rs2734831	2511	1	1
rs67800399	2606	1	1
rs12798900	2889	1	1
rs2734833	3187	1	1
rs7131440	3803	1	1
rs2587548	3895	1	1
rs2234690	4359	1	1
rs11214605	4494	1	1
rs1800498	4519	1	1
rs12800853	6407	1	1
rs1107162	7070	1	1
rs4938017	7822	1	1
rs7122246	8350	1	1
rs12364051	9207	1	1
rs2734838	9606	1	1

rs12363125	10191	1	1
rs4587762	10786	1	1
rs11214608	19248	1	1
rs11608185	1131	0.964	1
rs7131627	3722	0.964	1
rs2734835	4764	0.964	1
rs2734839	9617	0.964	1
rs11608109	7341	0.93	1
rs76208665	19995	0.927	0.963
rs2734837	9278	0.891	0.962

9. Discussion

9.1 RS1116313 by Mother's Education Interaction Predicts Trunk/Total Fat

After controlling for necessary covariates and family clustering, a mother's education by RS1116313 genotype interaction was found to predict trunk fat and total body fat. The same interaction, however, did not predict total calorie consumption. Therefore, tests of total calories mediating the relationship between the GxE interaction and body fat composition were not undertaken.

When probing the RS1116313 x mother's education interaction, homozygotes appeared to benefit from a mother's graduate school education whereas heterozygotes did not. It is possible that molecular heterosis can explain these effects on trunk and total body fat. Molecular heterosis is a phenomenon by which participants heterozygous for a specific polymorphism show a different effect (e.g., either a greater effect – positive heterosis, or a lesser effect – negative heterosis) for a trait than subjects homozygous for either allele who do not differ on that trait (Comings & MacMurray, 2000).

It is noteworthy that Comings had begun exploring molecular heterosis through his work on the DRD2 gene specifically (Comings, 1999). His review of these DRD2 studies of the RS1800497 SNP found a heterosis effect for impulsive, compulsive and addictive behaviors commonly present in such disorders as pathological gambling and ADHD. Comings found that participants heterozygotic for the RS1800497 polymorphism had the greatest number of DSM-IV criteria compared with their homozygotic counterparts (Comings & MacMurray, 2000). Moreover, later analyses

found the lowest D2 receptor density among heterozygotes (i.e., negative heterosis), suggesting that those heterozygous for the RS1800497 SNP may require greater reinforcement to meet thresholds (Comings, 1999).

Although no evidence supported a mother's education by RS1800497 SNP interaction in the current study, the mother's education by RS1116313 interaction may parallel Comings' DRD2 molecular heterosis findings. For example, although both homozygous groups reduced trunk and total body fat as one's mother's education increased, the heterozygotic group did not.

Few prior publications exist on the RS1116313 genotype. As noted earlier, two articles note its link with alcoholism, 'craving,' and DSM-IV criteria for dependence (Agrawal, et al., 2012; Bhaskar, et al., 2010), and one additional article found no association with addictive behaviors (Liu, et al., 2005). Although the first article did not specify which allele was linked, the latter found the T allele to be more common in individuals suffering from alcoholism. In contrast, this study revealed a heterosis pattern whereby the C/T carriers did not reduce trunk or total body fat in response to a high mother's education as homozygotes did.

An analysis of SNPs in high LD with the RS1116313 revealed 27 SNPs, seen in Table 24. A Medline search revealed few articles investigating any of the SNPs. One study found that RS1076563, also a DRD2 intron, was associated with smoking in 14 year-olds (Ducci, et al., 2011). Several studies investigated the RS1800498 SNP, also known as Taq1D, as an ancestry marker since it exhibits a significant allelic variety among racial/ethnic groups (Choudhry, et al., 2006; Martinez-Fierro, et al., 2009; Mez, et al., 2009; Saraswathy, et al., 2009). Again linking this genotype to addictive behavior, an

association between a haplotype which includes this SNP and alcohol and smoking behavior was identified (Preuss, Zill, Koller, Bondy, & Sokya, 2007).

Alternatively, a number of studies revealed negative findings. For example, several studies found no association with schizophrenia in an Indian population for several polymorphisms, such as RS12808482, RS11608185, and the Taq1D (Caprini, et al., 2011; M. Gupta, et al., 2009), although one earlier study had found a moderate association between the Taq1D genotype and treatment success in schizophrenia (Vijayan, et al., 2007). One study revealed no link for the Taq1D SNP with reward sensitivity in binge eating disorders (Davis, et al., 2008), another found no link with sensation-seeking for any of 40 SNPs in the DRD2 gene (Derringer, et al., 2010), and still another found no link with ADHD symptomatology among ADHD children and their families (Kollins, et al., 2008).

Given limited information about the RS1116313 genotype itself, one might look to previous research on the DRD2 gene itself in which this SNP resides to inform findings on this GxE effect on body fat composition. Previous research has suggested that the DRD2 gene has effects on a variety of behaviors including eating behavior that are moderated by early life stress (Berman & Noble, 1997; Madrid, et al., 2001; van Strien, et al., 2010). Thus, it was hypothesized in this study that DRD2 polymorphisms, moderated by early life stress, might affect eating behavior and predict uncontrolled eating among some individuals. This excessive eating was hypothesized to mediate increases in fat composition; however, the results of the current study suggest otherwise.

9.2 24-Hour Diet Recall Does Not Mediate Effects on Body Fat

A Mother's education by genotype interaction was not a significant predictor of total calorie consumption; however, the strong negative correlation between total calories and body fat suggested that the 24-hour diet recall may have not been an accurate measure. It is well known that adiposity is the result of an imbalance of energy intake and expenditure (American Association of Diabetes, 2012; Ekmekcioglu & Touitou, 2011; World Health Organization, 2012). Scientists have suggested that even affecting energy balance by 100 kcal per day could prevent weight gain in most of the population (Hill, Wyatt, Reed, & Peters, 2003), and one empirical study suggests that the imbalance required for weight gain might be as little as 10 kcal per day in one sample of middle-age women (Brown, Williams, Ford, Ball, & Dobson, 2005).

Considering that the current models predicting body fat composition by total calorie intake adjusted for two measures of physical activity, it would be hypothesized that models would reveal a positive association. Even when adjusted for a number of additional covariates including baseline age, race, sex, height, and physical activity, the current study found no relationship between total caloric intake and body fat composition. Since the caloric measure was only designed to measure one 24-hour period, it seems likely that this measured eating behavior might not accurately reflect regular eating patterns.

Indeed, underreporting of energy intake is very common (Trabulsi & Schoeller, 2001), and many studies have demonstrated a positive relationship between underreporting and obesity (Ferrari, et al., 2002; Johansson, Solvoll, Bjorneboe, & Drevon, 1998; Jonnalagadda, et al., 2000; Tooze, et al., 2004; Trabulsi & Schoeller, 2001).

Recent work suggests that financial incentives do not even improve accuracy (Hendrickson & Mattes, 2007). It appears that the 24-hour diet recall was probably not an accurate portrayal of dietary behavior in the current study; and therefore, future studies should either employ a more accurate diet recall method or seek a different method for exploring diet such as a metabolic blood screen.

It is also possible that the dietary recall was indeed a valid measure, and measures of total calorie consumption do not reliably predict trunk or total body fat composition. Given individual differences in the metabolism of dietary components (e.g., percent of calories from carbohydrates, protein, fat, and saturated fat), a post-hoc hypothesis tested whether percent of calories from dietary components instead of total calories mediated the effect of the RS1116313 by mother's education interaction on body fat composition. Models predicting percent of calories from dietary components by the RS1116313 by mother's education interaction were all non-significant, suggesting that the percent of calories from dietary components does not mediate the observed GxE effect on trunk and total body fat.

Apart from eating behavior (i.e., either total calories consumed or percent of calories from dietary components), other variables should be considered as potential mediators. Early life socioeconomic stress may interact with the RS1116313 SNP to either 1) affect a third variable such as exercise, which accounts for the changes in body fat composition or 2) affect metabolic changes unrelated to eating behavior that regulate adiposity. Post-hoc analyses in the current study suggested that leisure exercise, which is associated with trunk and total fat, is not the third variable mediating effects on body

fat, but HPA axis or sympathetic nervous system (SNS) function have not yet been explored as possible mediators.

9.3 DRD2 and Metabolism

Some evidence does suggest that metabolic changes may depend in part on DRD2 gene expression. One recent study suggests that DRD2-mediated neurotransmission is involved in the control of glucose and insulin metabolism (de Leeuw van Weenen, Parlevliet, et al., 2011). In this experiment, investigators found that they could induce or reduce insulin resistance in C57Bl6 mice via DRD2 antagonists or agonists respectively. The same researchers further clarified these findings with another rodent experiment demonstrating that a DRD2 antagonist even curtails the beneficial impact of calorie restriction in obese mice (de Leeuw van Weenen, Auvinen, et al., 2011).

Despite these findings arguing for the role of DRD2 expression in calorie consumption, findings in the same study reported that restricting access to a high-fat diet did not increase hypothalamic DRD2 binding capacity as expected. And a previous study by the same author found that a high fat diet induced insulin resistance but did not alter gene expression levels of DRD2 in rodents (de Leeuw van Weenen, et al., 2009). These findings suggest that DRD2 expression might affect dopaminergic function in ways that are not currently understood or perhaps that DRD2 effects on diet may vary by individual.

Still, previous studies supporting the importance of DRD2 in metabolic processes have shown that DRD2 agonists improve glucose and lipid metabolism in human patients with metabolic disorders (dos Santos Silva, et al., 2011; Yavuz, et al.,

2003), including preliminary results showing improved glucose metabolism in obese Type 2 diabetic individuals (Cincotta, Meier, & Cincotta, 1999). The mechanism of this effect may be via the autonomic nervous systems, as suggested by one study showing that a two-week treatment of DRD2 agonist may affect insulin resistance via suppression of noradrenergic outputs to peripheral tissues such as muscle, liver, and adipose tissue (Carey, Van Loon, Baines, & Kaiser, 1983).

Surwit et al. have repeatedly suggested a relationship between epinephrine, trunk fat, and dysregulated glucose metabolism (Surwit, Kuhn, Cochrane, McCubbin, & Feinglos, 1988; Surwit, et al., 2012; Surwit, et al., 2010). Building on much previous scholarship demonstrating that an accumulation of central adipose tissue is related to increased risk of diabetes (Bergman, et al., 2007), Surwit et al. have presented results suggesting that an interaction might exist between greater adipose tissue and greater epinephrine predicting higher fasting glucose (Surwit, et al., 2010). Moreover, they suggest that abnormal glucose metabolism may be the result of the adrenal medulla's failure to adapt to increasing levels of adiposity (Surwit, et al., 2012).

In summary, one possible mechanism of the GxE effect on body fat composition incorporates Surwit et al.'s theory and Carey's theory with what is known about DRD2 receptor expression. If mother's education is taken as a proxy for life stress with higher education associated with lower stress levels, it may be that some genotypes derive a greater benefit from a reduced stress environment, operationalized here as greater mother's education. Whereas homozygotes appear to benefit from a mother's graduate school education and reduced trunk and total body fat, heterozygotes of the RS1116313 SNP do not. Homozygotes might be able to increase DRD2 expression and consequently

reduce SNS activation, akin to the effect of a DRD2 agonist. The ultimate benefit may result in a reduction of adiposity and better regulation of glucose metabolism.

Heterozygotes may not be able to modulate receptor expression in response to a less stressful environment, and therefore their adiposity remains unchanged. Or alternatively, it may be that heterozygotes may have a predisposition to maintain homeostasis despite changes in childhood SES/stress. The specific effects of RS1116313 on glucose metabolism and whether adiposity antecedes glucose dysregulation or visa-versa could possibly be explored in future studies using the current dataset. Specifically, one might test if T/T and C/C carriers with a high mother's education have reduced SNS or HPA axis activation or both.

9.4 RS1800497 and RS1124492 by Mother's Education Interactions Predict Dietary Components

Although RS1800497 (i.e., Taq1A) and RS1124492 genotypes were not significant predictors of either total calorie intake or body fat composition, the SNPs were predictors of dietary components in post-hoc exploratory analyses. It is unclear how accurate these measures may be, given the suspected invalidity of the total calorie measurement from the 24-hour diet recall; however, apart from the volume of calories, it is possible that the dietary component data may still be valid and may explain the actual breakdown of types of calories consumed. Above, it was demonstrated that a mother's education by RS1800497 genotype predicted percent of calories from dietary fat and protein. A mother's education by RS1124492 genotype interaction predicted percent of calories from dietary fat.

According to a recent study, a higher frequency of the A allele is associated with obese BMI values in a sample of young Mexican-Americans (Duran-Gonzalez, et al., 2011). Although GxE interactions did not predict total calories or body composition, a mother's education by RS1800497 genotype interaction predicted percent of calories from dietary fat and protein.

Those same A allele carriers who were predisposed to obesity in a recent study consumed the lowest percent of calories from fat and the greatest percent in protein. Much of the interaction effects were driven by differences among A/A homozygotes. Those A/A individuals whose mother had a graduate school education consumed significantly greater calories from protein and less from fat. These A/A homozygotes are the same individuals found to have greater BMI in the Mexican-American sample above. Although these differences did not translate to either total calorie consumption or body fat distribution, our findings suggest that perhaps these A/A individuals may be predisposed to certain diets according to early life socioeconomic status. In a larger sample, these differences in diet might translate into differences in obesity status.

Since no studies have been published to date on the RS1124492, little can be inferred about the pattern of calorie consumption. Notably, among genotypes only the A/A homozygotes increased calories from fat as mother's education increased. There was a trend for A/A homozygotes with a high mother's education to consume the greatest calories from fat compared with all other genotype/mother's education combinations. Although two SNPs in the DRD2 gene (i.e., RS1800497 and RS1124492) predicted percent of calories from dietary fat, they produced very different patterns of fat consumption.

Whereas the RS1800497 A/A homozygotes consumed their peak calories from fat with a college-educated mother, the RS1124492 A/A consumed their peak calories from fat with a graduate school-educated mother. Reanalyzing this data by haplotypes or statistical combinations of SNPs might yield a more informative pattern of findings as Claude Bouchard (2012) has recently discussed. By creating a linear combination of SNPs, one might combine a greater volume of informative GxE data and perhaps make more generalizable inferences.

9.5 Main Effect of Mother's Education on Body Fat

Some researchers suggest that individuals may consume greater calories from fat and carbohydrates when exposed to a stressful environment (Dallman, 2003, 2010). Results for a main effect of mother's education predicting trunk and total body fat in several models suggest that one might find a main effect for mother's education predicting calories from fat and carbohydrates in a larger sample with a more accurate dietary measure. Despite uncertainties regarding the validity of the caloric data, in Figures 6 and 7 a gradual reduction of calories from fat is seen as mother's education increases. A gradual reduction of trunk and total body fat is seen as mother's education increases. Two significant main effects and one trend of mother's education predicting trunk fat was observed, and two significant main effects of mother's education predicting total body fat was observed, even after controlling for genetic effects.

Although several previous studies have shown a relationship between SES and obesity (Grafova, et al., 2008; Wang & Beydoun, 2007; Wardle, et al., 2002), one review points to several other studies that have not replicated these findings (Tamayo, et al.,

2010). Future work might seek to replicate previous findings suggesting an effect of early life SES on percent of calories from carbohydrates and fat, which in turn may predict body fat distribution. However, potential interactions between genotypes and early life SES measures should be taken into account first.

Initially, the hypothesis was that father's education would have a significant effect in interactions with DRD2 SNPs predicting body fat outcomes; however, mother's education ultimately emerged as a better predictor. Father's education was thought to affect a family's resources during critical periods early in life, yet a mother's education might actually have more impact on children if they are spending more time in the care of their mother.

Recent findings from the NHLBI Growth and Health Study from the USA found that the major factors best predicting change in BMI percentile among girls was family socio-economic position, specifically income and parent education (Rehkopf, Laraia, Segal, Braithwaite, & Epel, 2011). Moreover, this current study suggests that father's education may not be as important as mother's education in determining future obesity. For example, Currie et al. examined the relationship between father's occupation and items of 'family affluence' (e.g., car ownership, telephone ownership, and the child having his or her own unshared bedroom) and found associations to be moderate or weak (Currie, Elton, Todd, & Platt, 1997). This suggests that greater father's education may not necessarily translate to better living conditions or less SES/stress.

On the other hand, mother's education was a strong predictor of both obesity in males and females (Kautiainen, et al., 2009) and of physical activity in a review of 150 studies (Ferreira, et al., 2007). One study found a trend for an ethnicity by mother's

education by 5-HTTLPR genotype interaction predicting central nervous system serotonin turnover; no significant findings were reported for father's education (Williams, et al., 2003). It is possible that mother's education, more than father's education, predicts the SES/stress conditions more strongly associated with obesogenic environments, and this should be explored in future studies.

9.4 Limitations

Despite the extensive models explored in this research project, several limitations should be mentioned. Firstly as described above, the inaccuracy in the measure of total calories as indexed by a 24-hour diet recall limited the conclusions that could be drawn about total calories consumed as a mediator of trunk or total body fat. A more accurate measure of eating behavior or a more accurate blood test for inferring diet should be used in place of the current 24-hour diet recall measurement.

Given the choice of variables, some expectations are made about the constructs explored in these analyses. For example, it is possible that the measures of socioeconomic stress in this study did not capture early life stress as precisely as other measures would. As described in greater detail above, low socioeconomic status is related to a broad variety of stressful life conditions (Geronimus, 2000), perceived stress (Finkelstein, Kubzansky, Capitman, & Goodman, 2007), poor social skills and self-esteem (Lachman & Weaver, 1998), and poor future health (Cohen, et al., 2006). It may be that some of these correlated stress factors are more important than others in interactions with the RS1116313 SNP predicting obesity.

Measures that more accurately capture stress that is both acute (e.g., child abuse that is court-adjudicated) and time-limited (e.g., abuse limited to ages younger than 7 years old) may provide a more robust measurement of early life stress. These variables may provide a measure of stressful life experience that could more easily be contrasted with the daily stress experienced by average people and more accurately measured (e.g., according to legal charges or frequency of physical altercations).

However, despite its methodological usefulness, these types of indicators may offer a reduced applicability to the types of real life stress that average individuals experience in their life course. Since only a small fraction of the population reports this former type of severe stress, this measure may be less useful in predicting obesity in the general population. This 'efficacy' vs. 'effectiveness' debate has been extensively argued without apparent resolution in the public health literature (Glasgow, Lichtenstein, & Marcus, 2003; Hallfors, et al., 2006). Despite these debates, a methodological choice was made for the purposes of this study given the available variables and future replication studies should experiment with alternative measurements of early life stress, such as parenting styles (Fuemmeler, et al., 2012).

Another limitation of this SES/stress measure is the possibility that a third correlated variable might explain the observed significant GxE effect in the current study, although this is a possibility in any study. As just described, socioeconomic status co-occurs with many other factors including possibly better nutrition and better eating behavior among children. For example, higher maternal education was associated with less malnutrition and malnutritive stunted-growth in non-US populations (Abuya, Onsomu, Kimani, & Moore, 2011; M. C. Gupta, Mehrotra, Arora, & Saran, 1991; Urke,

Bull, & Mittelmark, 2011), a greater tendency to breastfeed (Skafida, 2009), a lower prevalence of emotional eating (Saxton, Carnell, van Jaarsveld, & Wardle, 2009), and more vegetables and less unhealthy foods consumed by 10-year old children (Cribb, Jones, Rogers, Ness, & Emmett, 2011). Instead of reduced socioeconomic stress, it is possible that increased maternal education, for example, is linked instead to a healthier diet among RS1116313 homozygotes. This study was designed only as a first step in exploring stress by gene interactions in obesity. Future studies will be necessary to identify which aspects of socioeconomic stress or its correlated factors might reliably interact with the RS1116313 SNP to predict obesity.

Although the larger sample includes almost 700 participants, due to missing data the final samples used for statistical analyses incorporated many fewer observations. As described above, not all participants were genotyped and not all participants were used for anthropometric measurements. The limitation of having smaller samples is witnessed in missing cells on several figures, the difficulty in finding significant differences between mean data points due to high standard error of measurement, and the inability to converge the interactive model predicting exercise as a mediator of body fat composition.

Fortunately, by using tertiles of mother's education, the majority of analyses were able to retain respectable cell sizes; yet, as a whole this study does not contain a large number of participants compared to average genetic association studies. As a result of this and the limited geographic or racial diversity in this sample, the findings in this study may not necessarily be generalizable to the larger population. However, it is hoped that in the future a larger sample such as Add Health or CARDIA might be used

to replicate this significant finding of a mother's education by RS1116313 interaction predicting body fat composition.

9.5 Future Directions

This study was able to investigate a number of hypotheses concerning GxE interactions in the development of DXA-scan-measured obesity; yet, this study might only be the first in a series of potential investigations seeking to uncover the stress by gene interactions behind the origins of obesity. In addition to suggestions for future directions already stated above, it is suggested that future studies incorporate more complex structural equation modeling. Statistical modeling used in this study controlled for family-level clustering, covariates, and class variables, but future analyses could theoretically conduct more intricate tests of the directionality of effects, tests of the appropriateness of latent class analysis for stress or genetic data, tests of the effect sizes of latent classes, and fit statistics for each model.

Additionally, future studies may conduct an analysis based on allelic frequency instead of genotype frequency. The current study sought to identify an interaction between parental education and the three genotypes associated with each SNP; however, interactions between parental education and the two alleles associated with each SNP might uncover different effects. Another method for investigating genetic effects on complex disease outcomes involves creating combinations of SNPs or also haplotypes as described recently by Bouchard (2012). Other researchers are publishing innovative techniques for combining and factor analyzing genetic polymorphisms (Cicchetti, Rogosch, & Oshri, 2011; Ihsan, et al., 2011). In time, these new techniques may

provide novel approaches to analyze multiple genes interacting with environmental exposures to predict complex disease outcomes like obesity.

Future work might also investigate Dallman's hypotheses (2010) regarding the dietary preference of some individuals when they are exposed particular types of stress. A more thorough and accurate study of diet might collect nutritive data at intervals to account for diet variability. Moreover, given the promising results obtained for mother's education by genotype interactions predicting dietary preferences, future studies might investigate this line of research further.

Given the potential link between DRD2 gene expression and glucose metabolism detailed above, future work might investigate not only the food items eaten but also differences in how these dietary components are metabolized depending on stress level and DRD2 genotype. It is possible that individuals may have dietary preferences, but their ultimate adiposity might be moderated by further gene by stress interactions.

Finally, future directions may include further analysis of parental education segmented in more than three categories. Given the small cell sizes in the current dataset, tertiles were necessary to conduct these GxE analyses; however, utilizing a greater number of parental education categories with a larger sample might allow investigators to conduct a more detailed analysis of the complex SES by genotype interactions and the effects of the RS116313 by mother's education interaction on SNS and HPA axis. This investigation may indeed be possible in the current sample since a number of metabolic measures are available.

9.6 Conclusions

Although this study cannot cover the entire range of possible questions about the etiology of obesity, it is hoped that this project might answer certain key questions that remain unanswered in the literature. For example, this study provides new information about how mother's education interacts with DRD2 to affect obesity. Specifically, this study suggests that a SNP on the DRD2 gene interacts with mother's education to predict trunk and total body fat. In the current analysis, it appears that this effect is not due to leisure activity and may not be associated with total calorie consumption. Instead, it may be that the interaction acts through the role of DRD2 in glucose metabolism, possibly interacting with the SNS or HPA axis to predict body fat.

More broadly, this study hopes to inform the larger literature on GxE interactions and obesity. To date, very few GxE studies have investigated the link between dopamine and obesity, despite many potential connections between the stress and the possible stress-relieving properties of food. It is hoped that this study will be part of a larger program of research seeking to uncover the complex etiology of obesity – an etiology that no doubt relies on a combination of both genetic and environmental factors.

10. References

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11. Biography

Michael Vicente Stanton was born in Bogota, Colombia and moved to Boston, MA shortly after where he was raised. He attended Milton Academy for secondary school and graduated in May 1998. He attended Brown University where he double-majored in Psychology and Africana Studies and graduated in May 2002. After working in consulting briefly, Michael worked at Harvard University Medical School's Division on Addictions for several years and published a number of research articles on gambling and alcohol studies. Subsequently, Michael spent over a year abroad on a US Fulbright grant in Senegal, West Africa where he studied coping and mental illness in rural and urban settings.

Michael is currently a Ph.D. Candidate in Duke University's Clinical Psychology program with a focus in Behavioral Medicine. He has published 11 articles thus far on socioeconomic stress, discrimination, genetics, and health. In addition to the Fulbright Student grant, he received a Fulbright extension grant, a four-year Duke Endowment Fellowship, Honorable Mentions from the National Science Foundation and the Ford Foundation, as well as grants from the American Psychological Association, the American Psychosomatic Society, Verizon/GTE Advanced Laboratories, and Brown University for his research.